Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

THERAPEUTIC DRUG MONITORING
CLINICAL GUIDE

Put science on your side.

Abbott
A Promise for Life

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

THERAPEUTIC DRUG MONITORING
CLINICAL GUIDE

Third Edition

Authors Michael Hallworth, BA, MA, MSc, FRCPath
Consultant Biochemist
Royal Shrewsbury Hospital
United Kingdom

Ian Watson, MSc, PhD, FRCPath
Consultant Biochemist and Toxicologist
University Hospital Aintree, Liverpool
United Kingdom

Editors David Holt, DSc, PhD
Director, Analytical Services International Ltd
Caterham, Surrey
United Kingdom

Susan Tett, PhD, BPharm(Hons), MPS
Professor, Deputy Executive Dean & Associate Dean (Research)
Faculty of Health Sciences, University of Queensland
Brisbane, Australia

Steven H. Wong, PhD, DABCC (TC), FACB
Professor of Pathology, Psychiatry and Behavioral Medicine,
and Population Health–Epidemiology
Director, Toxicology, TDM, Pharmacogenomics and Proteomics
Medical College of Wisconsin
Milwaukee, Wisconsin
United States

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

THERAPEUTIC DRUG MONITORING

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

- Why is TDM necessary?
- Which drugs should be monitored?
- Practical considerations
- Calculation of dosage adjustment
- Other approaches to optimizing therapy – pharmacogenetics and biomarkers
- Effectiveness of TDM – does it help patients?
- References
- Web sites

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is the use of drug concentration measurements in body fluids as an aid to the management of drug therapy for the cure, alleviation or prevention of disease.[1] It has long been customary to adjust the dosage of drugs according to the characteristics of the individual being treated and the response obtained. Physicians have been most ready to do this when the pharmacological response can be easily established by clinical means (eg, antihypertensive drugs, analgesics, hypnotics) or by laboratory markers (eg, anticoagulants, hypoglycemic agents, lipid-lowering drugs, hormone preparations). If there is a wide margin between the toxic dose and the therapeutically effective dose, then monitoring may be unnecessary (eg, penicillins). However where this is not the case and the drug's action cannot readily be assessed clinically (eg, in the prophylaxis of seizure or mania) or when toxic effects cannot be detected until severe or irreversible (eg, aminoglycoside antibiotics, immunosuppressants), then dosage individualization is much more difficult, though no less important. TDM now has an established place in enabling optimization of therapy with such agents; although it must be emphasized that clinical and other criteria remain important, TDM should never be the sole basis for individualization of therapy. TDM has been established for a tightly defined group of drugs. It must be considered as a process where it (i) begins with a clinical question, (ii) continues by devising a sampling strategy to answer that question, (iii) determines one or more drug concentrations using a suitable method, and (iv) interprets the results appropriately.

TDM has been routinely practiced in clinical laboratories since the mid-1970s, following initial research work showing its potential value. Buchthal[2] showed in 1960 that there was a relationship between plasma concentrations of phenytoin in patients being treated for epilepsy, and the degree of seizure control attained. And Baastrup and Schou demonstrated the relationship between plasma concentration and pharmacological effect for lithium in 1967.[3] This work coincided with the rise of clinical pharmacology as an independent discipline during the 1960s, and the development of the fundamental concepts of pharmacokinetics and pharmacodynamics.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

The scene was thus set for the surge of publications in the early 1970s on improving individualization of therapy by the monitoring of drug concentration and appropriate adjustment of dose – the beginnings of TDM as we know it. The remaining barrier to widespread adoption of the concept, the availability of appropriate analytical methods, was removed during the 1970s by the development of commercially available homogeneous immunoassays for therapeutic drugs. The ability to provide accurate and precise results simply and quickly resulted in the explosive growth of TDM applications in the second half of the 1970s.

WHY IS TDM NECESSARY?

As stated above, there are a number of drugs whose desired (or toxic) effects cannot readily be assessed clinically, but are related to the amount of drug in the body. In such cases, the logical approach to control the effect of the drug is to limit the amount that is given to the patient. Pragmatically this can be done by using standard doses that will produce a satisfactory response in the majority of patients. This historical approach has been widely used in medicine and is undoubtedly effective for a large number of drugs, eg, penicillins. The advent of pharmacogenomics is changing the crude “one dose fits all” paradigm and will be discussed further later in this chapter.

For many (but not all) drugs, the primary determinant of clinical response is the concentration that can be achieved at the site of action (the cell receptor, locus of infection, etc). Often, wide variations in drug concentration above a minimum or threshold level will make little difference to the clinical effect. However, for some drugs the desired effect (and various unwanted effects) may be very sensitive to the drug concentration at a given time. Dr Bernard Brodie suggested in a keynote lecture given in 1967 that the marked heterogeneity of biological species with regard to drug metabolism meant that it would be preferable to relate drug effects to the plasma drug concentration rather than the dose.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

The problem with an approach based on standard dosing for some drugs is illustrated in Fig 1.1, which shows the frequency distribution of plasma phenytoin concentrations among 200 ambulatory patients chronically treated with 300 mg/day.[4] If the clinically accepted therapeutic range for phenytoin is 20-80 µmol/L (5-20 mg/L) a large number of patients receiving the standard dose have plasma phenytoin concentrations below those said to be effective. Conversely, a minority has concentrations significantly above the generally accepted range and may be exhibiting symptoms of toxicity. The steady-state phenytoin concentration in a given patient clearly cannot be predicted from the dose. This is due to inter-individual variation in the processes which are involved between the prescribed drug and that drug achieving an effective concentration at its site of action. These processes are summarized in Fig 1.2 and are conveniently divided into pharmacokinetic factors and pharmacodynamic factors. Essentially, pharmacokinetics may be defined as what the body does to drugs (the processes of absorption, distribution, metabolism and excretion) and pharmacodynamics as what the drugs do to the body (mechanisms of drug action and biochemical/pathophysiological effects such as tissue responsiveness, presence of other drugs and disease states). A detailed discussion of pharmacokinetic and pharmacodynamic processes is outside the scope of this monograph, and standard texts may be consulted.[5]

Distribution of plasma phenytoin concentrations

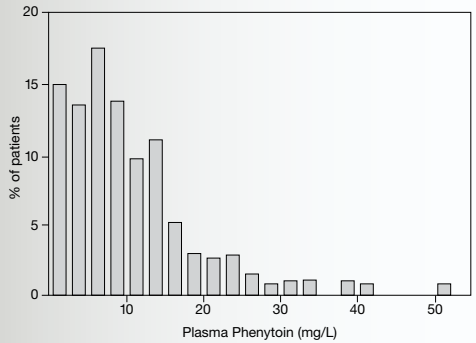


Figure 1.1 Frequency distribution of plasma phenytoin concentrations in 200 adult outpatients taking phenytoin (300 mg/day).(Possibly partially influenced by CYP2C9 and CYP2C19 variations.) Koch-Weser J. Serum drug concentrations in clinical perspective. Richens, A., Marks V. (eds). *Therapeutic Drug Monitoring*. Edinburgh: Churchill Livingstone 1981:1-22 (with permission).

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

Processes involved in drug handling

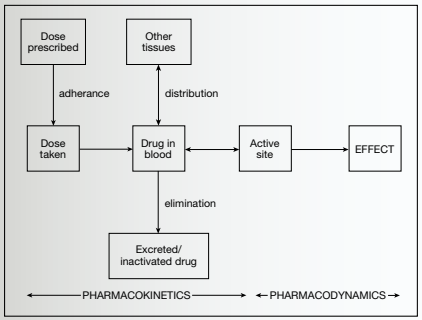


Figure 1.2 Processes involved in drug handling

WHICH DRUGS SHOULD BE MONITORED?

Drug concentration monitoring is neither feasible nor warranted for all drugs. Serum concentration monitoring is valuable in measuring the clinical effectiveness of drugs in the following circumstances:

When there is poor correlation between dose and clinical effect

Self-evidently, if the dose is a good predictor of the pharmacological effect, then dose can be used to monitor therapy and TDM is not normally required. TDM is primarily of potential benefit where there is poor correlation between dose and effect (wide inter-individual pharmacokinetic variation).

When there is a narrow concentration interval between therapeutic and toxic effects

The *therapeutic index* (therapeutic ratio, toxic-therapeutic ratio) for a drug indicates the margin between the therapeutic dose and the toxic dose: the larger, the better. For most patients (with the exception of those who are hypersensitive) penicillin has a very high therapeutic ratio. It is safe to use in much higher doses than necessary to treat the patient satisfactorily, with no necessity to check the concentration attained. However, for other drugs (eg, anticoagulants, aminoglycoside antibiotics, anti-neoplastic drugs, immunosuppressants, cardiac glycosides) the margin between desirable and toxic dose is very small and monitoring is valuable in achieving effective concentrations without systemic toxicity.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

When there are no good clinical markers of effect
TDM is clearly of little value when the desired effect and any associated adverse effects can readily be quantitated by simple clinical measurements, (eg, blood pressure in the case of antihypertensive agents or plasma glucose concentration for oral hypoglycemic drugs).

When plasma concentration shows a good correlation with clinical effect
This is the fundamental condition which must be fulfilled if TDM is to be practical for a particular drug. The concentration measurements must give accurate information about the biological effect, otherwise they are of no value and may even be misleading. Plasma or blood concentrations should correlate well with effect or toxicity, and thereby define the therapeutic window and allow titration of the dose to achieve a given effect. Demonstration of a close concentration-effect relationship requires that (i) there is minimal inter-individual pharmacodynamic variability, (ii) no active metabolites contribute to the biological effect but are not measured in the assay system, and (iii) a reversible mode of action at the receptor site. This latter relationship ensures that the intensity and duration of the response is temporally correlated with the drug concentration at the receptor site. (The exception to this general rule may be some anti-cancer agents,
where the action of the drug is irreversible but an index of the body's total exposure to the drug may predict subsequent response.)

The list of drugs which fulfills the criteria listed above is small. Phenytoin and lithium are probably the best and earliest examples of drugs that meet all the criteria and for which TDM is essential. The aminoglycoside antibiotics, chiefly gentamicin and tobramycin, also qualify on all counts. Theophylline meets most criteria. Although its clinical effects are slightly easier to assess, in adults at least, its clinical use continues to decline. A number of other frequently monitored drugs fail to meet one or more criteria completely. Thus, the effectiveness of TDM as an aid to management is therefore severely reduced. The concentration-effect relationship for carbamazepine is not always straightforward because of the presence of active metabolites. Digoxin fulfils most of the criteria, but with some doubt about the concentration-effect relationship.

THERAPEUTIC DRUG MONITORING

INTERACTIVE CLINICAL GUIDE

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

The evidence for many drugs is based more on practical experience than well-designed studies. However, when the immunosuppressant drug cyclosporine was introduced into clinical practice, considerable effort was invested in demonstrating the beneficial outcomes associated with effective TDM; this has provided a model for subsequent immunosuppressants eg, tacrolimus, sirolimus and mycophenolate. Similar evidence is accumulating to support the benefit of TDM for anti-retroviral drugs.

The drugs listed in this monograph are the main drugs for which TDM has been shown to have clinical value.

PRACTICAL CONSIDERATIONS

Once the narrow range of drugs for which therapeutic drug monitoring can provide useful information has been defined, it should not be assumed that TDM is therefore required for all patients receiving these drugs. For a concentration measurement to be applied effectively to improve patient care, four criteria must be satisfied on each occasion a sample is taken. These are:

A rational indication for the request (a clinical question)

The first essential for making effective use of any laboratory test is to be clear from the onset which question is being asked. This is particularly true of TDM requests, and the widespread failure to define the indication for analysis is at the root of most of the problems faced by TDM services. If the question is not clear, or if it is the wrong question, then the answer is of little value.

The main reasons for measuring drugs in plasma may be summarized as:

(a) To ensure that sufficient drug is reaching the drug receptor to produce the desired response (which may be delayed at onset)

(b) To ensure that drug (or metabolite) concentrations are not so high as to produce symptoms or signs of toxicity

(c) To guide dosage adjustment in clinical situations in which the pharmacokinetics are changing rapidly (eg, in neonates, children or patients in whom hepatic or renal function is changing)

(d) To define the pharmacokinetic parameters and concentration-effect relationships of new drugs

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

Accurate patient information
Accurate information about the patient (name, identification number, age, gender and pathology), the drug therapy (dose, formulation and route of administration, length of therapy, date and time of last dose), the specific question to be investigated and the date and time of the sample are essential for proper interpretation. These should be provided on the request form. Additional information such as the patient's weight, renal and hepatic function and other prescribed medication may also be required in many circumstances. These requirements have led many hospitals to design request forms specifically for TDM analyses. The increasing use of computerized order-entry systems means that essential items of information can be made mandatory at the point of requesting. These can be linked to rule-bases to ensure appropriate requesting and to improve use of TDM services.

An appropriate specimen
An appropriate specimen is obviously a prime necessity for effective TDM. Serum or plasma samples are normally used, although whole blood is the preferred matrix for many immunosuppressive drugs (eg, cyclosporine) as the drug is concentrated in red cells.

Timing of the specimen is also important. For TDM to be meaningful, the patient should be in steady-state on the present dose of the drug. However, when suspected toxicity is being investigated, waiting to attain steady-state is clearly contraindicated. The time taken to reach steady-state is determined by the elimination half-life of the drug. In practice, samples are taken after drug dosing has continued for at least four half-lives.

The plasma concentration after 3.3 half-lives is 90 percent of the predicted steady-state. This may be taken as the minimum time for sampling after starting the drug or changing the dose. For drugs with a long half-life (eg, digoxin, phenobarbitone), two weeks or more may be required before steady-state samples can be taken, especially if renal function is poor and the drug is renally excreted (eg, digoxin).

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

In the neonate, the rapidly changing clinical state, degree of hydration and dosage requirements make the idea of steady state a theoretical concept rather than an attainable goal in many cases. There is little value in delaying concentration measurements for such a hypothetical steady-state to be established.

A further requirement for many drugs is to take samples at the appropriate time following the last dose. Serum digoxin concentrations do not reflect tissue concentrations for at least six hours following dosing due to continuing distribution, and specimens for digoxin analysis should not be taken during this period.

The size of the fluctuations in plasma concentration between doses obviously depends on the dosage interval. Frequent dosing avoids large peaks and transient toxic effects. But this practice is unpopular with patients, difficult to comply with, and more likely to lead to medication errors. Less frequent dosing gives rise to large fluctuations in concentration. To some extent, these opposing considerations can be reconciled with the use of sustained-release preparations.

There is no single optimum time for taking samples in relation to dose.
The most reproducible time to take measurements is immediately pre-dose (trough concentration), when the lowest levels in the cycle will be obtained. This is best if an indication of drug efficacy is required. This sample will show least between-sample variability in patients on chronic therapy. The use of peak and trough concentrations for detecting toxicity of aminoglycoside antibiotics has become less relevant with once-daily dosing regimens, but sampling at two hours post dose for cyclosporine has become a common and effective TDM technique. This type of sampling in the absorption/distribution phase is highly sensitive to accurate determination of sampling time in relation to dose. The average steady state concentration may be obtained by taking samples approximately midway between doses.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

How often drugs should be monitored will also depend on the question to be answered and the clinical situation of the patient. Daily monitoring may be necessary in critically ill patients with rapidly changing clearance, for example with aminoglycoside antibiotics. Dosage requirements for immunosuppressive drugs vary markedly in the early days and weeks post-transplantation, and frequent monitoring is normally required. At the other end of the scale, stable patients on long-term anticonvulsant or antidepressant therapy may need little or no concentration monitoring in the absence of complications.

Regular monitoring is useful (i) when optimizing dosage initially, (ii) when other drugs are added to or subtracted from a regime, to guard against known or unexpected interactions, or (iii) when renal or hepatic function is changing.

Correct interpretation and appropriate response

Even if a relevant question has been formulated, an appropriate specimen taken and an accurate result obtained, the whole exercise is valueless unless the result is correctly interpreted and any necessary action taken. Interpretation of drug concentrations requires knowledge of the pharmacokinetic and pharmacodynamic factors affecting the drug in question, and may demand considerable expertise. Unfortunately, without effective educational programs, users of TDM services frequently interpret results simply by comparing them with the target range and then either do nothing or react to bring the levels closer to the quoted range. Much harm can be done by this process, as it is frequently forgotten by clinicians, as well as by laboratory workers that the aim of the TDM process is to ameliorate the patient's symptoms rather than to get drug levels into a particular range.

The target range is a synthesis of two concepts — the minimum effective concentration for a drug and the maximum safe concentration. Between these limits, the majority of patients should experience maximum therapeutic benefit at minimal risk of toxicity and undesirable side effects. However, this simple theory breaks down in a number of important respects, and the target range must always be considered as an adjunct to clinical judgment and not a substitute for it. For this reason, the term *target range* is preferred to the older term *therapeutic range.*

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

The optimum range of drug concentrations for a particular patient is a very individual matter, depending to some extent on the severity of the underlying disease process. This fact does not undermine the value of TDM, but does require a clear understanding of why an individual request has been ordered and how it can be interpreted in the light of the patient's condition. There is no reason to monitor drug concentrations in a patient who is clinically stable and not showing symptoms of toxicity, except to establish a baseline, in case any problems are subsequently encountered.

Difficulties arise when, having made a measurement for no particularly good reason on a stable patient, the clinician discovers that the result is outside the target range and feels compelled to do something about it. In one of the earliest papers on TDM, Koch-Weser[6] wrote: "Therapeutic decisions should never be based solely on the drug concentration in the serum." The cardinal principle, oft repeated but still forgotten, is to *treat the patient rather than the drug concentration.*

Drug concentrations above the target range do not invariably require a reduction in dosage. For immunosuppressants it may be necessary in some patients to run levels above the target range to avoid rejection of a heart transplant. For other drugs it may be that if the patient is symptom-free, a careful search for signs of toxicity should be made. If no evidence is found, the patient may be best served by doing nothing. Although for some drugs (eg, phenytoin), continued monitoring for the development of long-term undesirable effects is advisable. Similarly, drug levels below the target range in a patient who is well, and free from symptoms, do not require an increased dose,[7] although in some cases (eg, digoxin), they may provide evidence that the drug is no longer necessary and stopping it under medical supervision is worth trying.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

CALCULATION OF DOSAGE ADJUSTMENT

Drug concentration measurement in individual patients provides a surrogate endpoint for response, and may therefore be used to guide dosage adjustment toward the optimal dose for a particular patient. Several available approaches allow use of the serum concentration obtained on a known dosage regime to predict the new dosage regime. These approaches will deliver optimal drug concentrations and full details may be found in standard pharmacokinetic texts.[5]

The most straightforward approach for drugs following first-order (linear) pharmacokinetics is to use simple proportionality. A new dose D_N can be calculated from the present dose D, the actual plasma concentration C and the desired plasma concentration C_N as follows:

$$D_N = \frac{D}{C} . C_N$$

For practical purposes, trough concentrations rather than steady-state concentrations are normally used. It must be recognized that when a single dose/concentration data pair is being used in such calculations, great weight is being placed on a single measurement. There are a number of implicit assumptions, namely that (i) the correct dose was given at the stated time, (ii) an accurate measurement of the drug concentration was made, (iii) an accurate recording of the time of sample collection was made, and (iv) steady-state concentrations have been achieved. Errors in any of these may result in erroneous dosage predictions.

For drugs that do not exhibit first-order kinetics (eg, phenytoin), or where the response to inappropriate plasma concentrations is to alter the dose interval rather than the dose amount (eg, for aminoglycosides), published nomograms are available to facilitate dose adjustment. (Refer to the Hartford nomogram for gentamicin administration.)[8]

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

Software exists to assist dosage prediction and ranges from automated forms of simple pharmacokinetic equations to more sophisticated systems that employ population pharmacokinetics, Bayesian statistical theory, maximum likelihood estimations and neural networks. When serial serum concentrations are measured, it is possible to fit pharmacokinetic models to the measured concentration versus time data and estimate pharmacokinetic parameters for the individual patient. A limitation of this approach is that it requires multiple blood samples, which is not always feasible or cost-effective for routine patient care.

An alternative approach is to use Bayesian principles for parameter estimation.[9] In addition to measured serum concentrations, the Bayesian approach uses what is already known about a drug's pharmacokinetic parameters in patients similar to the individual being evaluated (population pharmacokinetics). These *a priori* assumptions are then combined with one or more actual concentration-dose pairs to give a refined best estimate for the individual's pharmacokinetic parameters, which can be used to predict future dose requirements. This approach forms the basis of many neural networks or other computer programs for dosage optimization. Such systems have been described for a variety of drugs[10] and in many cases made commercially available. They have undoubted value in experienced hands, particularly when complex drug regimes are involved. However, care is needed in their use, particularly in the hands of people who do not have a good understanding of the underlying principles and limitations. The output from dosage prediction programs is only as good as the data fed into them, and dose predictions should always be checked by an experienced practitioner before being used clinically.

OTHER APPROACHES TO OPTIMIZING THERAPY — PHARMACOGENETICS AND BIOMARKERS

We began this chapter by defining TDM as the use of drug or metabolite measurements in body fluids as an aid to monitoring therapy. In recent years, other methods of controlling drug therapy have been introduced, and though they do not fit the strict definition of TDM, they merit discussion as they become increasingly important. Pharmacodynamic monitoring is the study of the biological effect of a drug at its target site, and

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

has been applied in the areas of immunosuppressive therapy and cancer chemotherapy. For example, the biological effect of the immunosuppressant cyclosporine can be assessed by measuring the extent of inhibition of calcineurin phosphatase, or the interleukin-2 concentration of peripheral blood lymphocytes. The main disadvantage of pharmacodynamic monitoring is the fact that the assays involved are often significantly more complex and time consuming than the measurement of a single molecular species by chromatography or immunoassay.

Any biochemical measurement that can be used to determine efficacy, extent of toxicity, or individual pharmacodynamics for a therapeutic agent, is termed a therapeutic *biomarker.* Biomarker monitoring can provide an integrated measure of all biologically active species (parent drug and metabolites), so target ranges can be defined more closely. In addition, biomarkers are often free from the matrix and drug disposition problems that bedevil TDM in some areas, notably immunosuppressants.

Pharmacogenetic studies (studies of hereditary influences, including ethnicity, on pharmacological responses) have clear and wide-ranging clinical relevance. The enzymes that are responsible for metabolism of drugs and other compounds exhibit wide inter-individual variation in their protein expression or catalytic activity, resulting in different drug metabolism phenotypes between individuals. This variation may arise from transient effects on the enzyme, such as inhibition or induction by other drugs, or may be at the gene level and result from specific mutations or deletions. *Pharmacogenetic polymorphism* is defined as the existence in a population of two or more alleles (at the same locus) that result in more than one phenotype with respect to the effect of a drug. The term *pharmacogenomics* has recently been coined to describe the range of genetic influences on drug metabolism and its application to the practice of tailoring drugs and dosages to individual genotypes to enhance safety and/or efficacy. This practice — often called “Personalized Medicine” — undoubtedly represents a massive growth area for 21st century medicine.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

Determination of an individual's ability to metabolize a specific drug, may be performed by either administering a test dose of the drug or a compound metabolized by the same enzyme system (phenotyping) or by specific genetic analysis (genotyping). The phenotyping and genotyping results can inform and improve the clinician's ability to adjust drug dosing according to the specific requirements of the individual patient. For example, a number of enzymes of the cytochrome P450 superfamily show genetic polymorphisms that account for differences in clinical response. The CYP2D6 isoform has more than 75 allelic variants, and metabolizes a range of drugs widely used in medicine, including many anti-arrhythmics and antidepressants. Debrisoquine is also a substrate for this isoform. Debrisoquine hydroxylase activity is determined by the rate of metabolism of a test dose of debrisoquine. This has been used widely for the determination of CYP2D6 phenotype and the differentiation of poor metabolizer (PM), extensive metabolizer (EM) and ultra-extensive metabolizer (UEM) phenotypes. Since debrisoquine is no longer available, dextromethorphan has replaced it as a probe drug for clinical use. Alternatively, genetic analysis can be used to define the CYP2D6 phenotype and identify the alleles associated with the PM phenotype (of which the most common are CYP2D6 *3, *4, *5, *6 and *7). Once determined, the phenotype or genotype can be used to guide dosing for any of the drugs metabolized by the CYP2D6 isoform.

The clinical applications of pharmacogenomics are extensive. Some examples are in anticoagulation (polymorphism of the CYP2C9 and VKORC1 genes), oncology (thiopurine methyltransferase isooforms and the serum Her2/neu receptor), psychiatry (CYP2D6 isoforms), epilepsy, pain control and other areas.

The combination of classical TDM, pharmacodynamic biomarkers and pharmacogenetics will undoubtedly accelerate the development and facilitate the clinical use of drugs, and will have a major role in delivering therapeutic efficiency and improved patient outcome with less need for plasma concentration monitoring.[11] However, integrating the information available from all three strands is a complex challenge which will require sophisticated decision support software and effective strategies for presenting the information in an

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

accessible format to those responsible for patient care. Pre-treatment pharmacogenetic profiling will allow identification of individuals who are likely to be particularly susceptible or resistant to a proposed treatment strategy, allowing better choice of starting dose or the use of a different drug. However, pharmacodynamic factors such as age, disease and other drugs mean that pharmacogenetics can never tell the whole story. Thus, biomarkers of effect and drug or metabolite concentration measurements will still be needed to complete the picture and deliver truly personalized therapeutics.

EFFECTIVENESS OF TDM – DOES IT HELP PATIENTS?

In an era of evidence-based medicine the lack of early studies into the efficacy of TDM has undermined its informed use.[12] The studies that have accompanied the development and effective utilization of immuno-suppressants[13] and more recent studies on aminoglycosides[14-15] have proven that properly applied TDM is effective and that the consequences of not performing adequate TDM for this class of drugs are dire. The lesser impact in other areas of TDM emphasizes the need for clinical judgment for effective application,[15] rather than uncritical ticking off of boxes.

In some surveys, two-thirds or more of requests made to TDM services have been shown to be inadequately thought out, badly executed or misinterpreted.[16] Requesting clinicians are frequently unclear as to when TDM would be helpful, and reluctant to pay proper attention to the results once obtained. The consequence of this has been an increasing workload for analytical laboratories and considerable waste of analytical and financial resources, plus diminished standards of patient care and an understandable degree of cynicism about the whole process. It is now clear that the availability of accurate TDM data does not in itself improve symptom control or reduce the incidence of toxicity in themselves. As long ago as 1985, in an editorial on TDM, *The Lancet*[17] noted that "If plasma drug assays are to be done, they must be accompanied by some form of education system that tells the prescribing doctor the meaning of the result and what steps should now be taken." This statement remains as true today as it was when it was written.

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

REFERENCES

1. Marks V. A historical introduction. In: Widdop B, (ed.) *Therapeutic Drug Monitoring.* Edinburgh: Churchill Livingstone; 1985:3-15.
2. Buchthal F, Svensmark O, Schiller PJ. Clinical and electroencephalographic correlations with serum levels of diphenylhydantoin. *Arch Neurol.* 1960;2:624-631.
3. Baastrup PC, Schou M. Lithium as a prophylactic agent. *Arch Gen Psychiatr.* 1967;16:162-172.
4. Koch-Weser J. Serum drug concentrations in clinical perspective. In: Richens A, Marks V, eds. *Therapeutic Drug Monitoring.* Edinburgh: Churchill Livingstone; 1981:1-22.
5. Burton ME, Shaw LM, Schentag JJ, Evans WE. *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring.* 4th ed. Philadelphia: Lippincott, Williams & Wilkins, 2006.
6. Koch-Weser J. Drug therapy: serum drug concentrations as therapeutic guides. *N Engl J Med.* 1972;287:227-231.
7. Woo E, Chan YM, Yu YL, et al. If a well-stabilized epileptic patient has a subtherapeutic antiepileptic drug level, should the dose be increased? A randomized prospective study. *Epilepsia.* 1988;29:129-139.
8. Nicolau DP, Freeman CD, Belliveau PP et al. Experience with a once-daily aminoglycoside program, administered to 2,184 adult patients. *Antimicrob Agents Chemo.* 1995;29:650-655.
9. Thomson AH, Whiting B. Bayesian parameter estimation and population pharmacokinetics. *Clin Pharmacokinet.* 1992;22:447-467.
10. Yamamura S. Clinical application of artificial neural network (ANN) modeling to predict pharmacokinetic parameters of severely ill patients. *Adv Drug Deliv Rev.* 2003;55:1233-1251.
11. Clark W, McMillin G. Application of TDM, pharmacogenomics and biomarkers for neurological disease pharmacotherapy: focus on antiepileptic drugs. *Personalized Medicine.* 2006;3:139-149.
12. Schumacher GE, Barr JT. Total testing process applied to therapeutic drug monitoring: impact on patients' outcomes and economics. *Clin Chem.* 1998;44:370-374.
13. Tsunoda SM, Aweeka FT. The use of therapeutic drug monitoring to optimize immunosuppressive therapy. *Clin Pharmacokinet.* 1996;30:107-140.

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

14. Binder L, Schiel X, Binder C, et al. Clinical outcome and economic impact of aminoglycoside peak concentrations in febrile immuno-compromised patients with hematologic malignancies. *Clin Chem.* 1998;44:408-414.
15. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systematic review. *Ther Drug Monit.* 2005;27:10-17.
16. Hallworth MJ. Audit of therapeutic drug monitoring. *Ann Clin Biochem.* 1988;25:121-128.
17. Editorial. What therapeutic drugs should be monitored? *The Lancet.* 1985;ii:309-310.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OVERVIEW

WEB SITES

The International Association of TDM and ClinicalToxicology:
http://www.iatdmct.org/

Cytochrome P450 drug interaction table from Indiana University (Ed. David Flockhart):
http://medicine.iupui.edu/flockhart/table.htm

Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee at Karolinska Institute:
http://www.imm.ki.se/CYPalleles/

Talking glossary of genetic terms: National Human Genome Research Institute:
http://www.genome.gov/glossary.cfm

Laboratory Medicine Practice Guidelines Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice. Edited by Roland Valdes, Jr., Deborah Payne, and Mark W. Linder:
http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/LAACP/Documents/PGx_Guidelines.pdf

Personalized Medicine Coalition:
http://www.personalizedmedicinecoalition.org/

President's Council of Advisors on Science and Technology report, Priorities for Personalized Medicine.2008.
http://www.whitehouse.gov/administration/eop/ostp

Leavitt, M. September 2007 report on Personalized Health Care: Opportunities, Pathways, Resources.
http://www.hhs.gov/myhealthcare/news/phc-report.pdf

FDA-CDRH's guidance for Pharmacogenetic Tests and Genetic Tests for Heritable Markers, 2007.
http://www.fda.gov/downloads/Medical Devices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071075.pdf

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES

PREFACE

The following drug profiles contain data which have been compiled from various reference sources and the clinical experience of the contributors.

"Usual dosages" reflect those considered most likely to achieve the desired serum concentrations, in patients with normal renal and hepatic function. When variable dosages are recommended for different patient groups, these have been represented diagrammatically.

Other parameters such as the usual dosing interval, time-to-peak concentration, time to steady-state serum concentration, elimination half-life, and protein binding are described for patients with normal organ function and average pharmacokinetic characteristics.

The therapeutic ranges quoted provide guidelines as to the patient drug concentrations which are expected to achieve optimal therapeutic effect. These therapeutic ranges are visualized as a green shaded area on the therapeutic range diagram lying between the subtherapeutic (blue) concentration and the potentially toxic (red) drug concentration.

Only a partial list of toxic effects and factors affecting drug concentrations are provided. These lists are not intended to be comprehensive. For more detailed information on individual drug preparations and characteristics, the manufacturer's package insert and the current medical literature should be consulted.

The purpose of this manual is to assist clinicians in the exercise of their independent professional judgment in the light of available clinical information. Although the information contained in this manual has been obtained from highly reputable sources and is believed to be accurate in accordance with currently available information, neither the authors, the editors, nor Abbott Laboratories assume any liability in connection with the use of

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES

specific information contained herein. Complete information concerning clinical indications, dosages, mechanisms of action, modes and timing of elimination, and toxic effects of therapeutic drugs available from the drug manufacturer should always be consulted.

ADDICTION THERAPEUTICS
Buprenorphine
Methadone

ANALGESICS
Acetaminophen
Acetylsalicylic Acid

ANTIBIOTICS
Aminoglycosides
Amikacin
Gentamicin
Tobramycin

Other Antibiotics
Teicoplanin
Vancomycin

ANTIEPILEPTICS
Carbamazepine
Ethosuximide
Felbamate
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital/Primidone
Phenytoin/Fosphenytoin
Pregabalin
Tiagabine
Topiramate
Valproate
Vigabatrin
Zonisamide

ANTINEOPLASTICS
Methotrexate

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES

BRONCHODILATOR, ANALEPTIC
Theophylline
Caffeine

CARDIAC AGENTS
Anti-Arrhythmics
Amiodarone
Disopyramide
Lidocaine
Procainamide/Napa

Cardiac Glycosides
Digitoxin
Digoxin

IMMUNOSUPPRESSIVE AGENTS
Ciclosporin/Cyclosporine
Mycophenolate
Sirolimus
Tacrolimus

PSYCHOACTIVE AGENTS
Tricyclic Antidepressants

Amitryptiline

Others
Chlorpromazine
Clozapine
Fluoxetine
Haloperidol
Lithium

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Addiction Therapeutics

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

- Buprenorphine
- Methadone

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

BUPRENORPHINE

CLINICAL USE
- Adjunct treatment of opioid dependence
- Analgesia

USUAL DOSE AND DOSE INTERVAL
- Opioid dependence: 0.8-4 mg/d sublingually, adjusted according to response to a maximum of 32 mg/d
- Analgesia: 0.2-0.4 mg every 6-8 h; children age-dependent, confirm local practice

FACTORS AFFECTING CONCENTRATION
- Partial μ agonist/antagonist
- Twenty times more potent as an analgesic than morphine
- Norbuprenorphine is the main metabolite by CYP3A4
- Norbuprenorphine metabolite is present in 20 times the concentration of buprenorphine in urine and is the target analyte

TOXIC EFFECTS
- Buprenorphine has abuse potential, there is a risk of death; this may be potentiated by other drugs. There appears to be a particular risk associated with benzodiazepine use
- Withdrawal symptoms
- GI disturbances

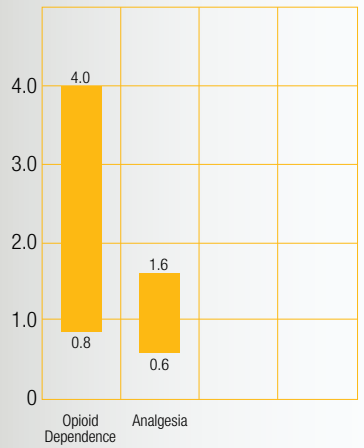
MONITORING THERAPY
- Monitoring of plasma concentrations has not been validated yet
- Confirmation of the norbuprenorphine metabolite in urine is a check on adherence

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	0.5 h (sublingual preparation)
Route of elimination	Hepatic metabolism (<1% excreted renally)
Elimination half-life	24-44 h (shorter in IV dosing)
Time to steady state	~10 days of chronic dosing
Protein binding	~96%
Target range	Threshold effect is said to be 0.7 ug/L (1.5 nmol/L)

TYPICAL ADULT DOSES (mg/d)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

METHADONE

CLINICAL USE

- Adjunct in treatment of opioid dependence
- Severe pain

USUAL DOSE AND DOSE INTERVAL

- Opioid dependence: Initially 10-40 mg daily as an oral solution, increasing by up to 10 mg/d, but no more than 30 mg in a week, until no signs of withdrawal: typically 60-120 mg/d
- Analgesia: 5-10 mg every 6-8 h, if for prolonged use twice daily

FACTORS AFFECTING CONCENTRATION

- Prescribed as a racemate: R-isomer is 30 times more active than the S-isomer as a μ receptor agonist
- R-isomer effective analgesic
- Enzyme-inducing drugs increase clearance
- Urine pH affects excretion: acid faster clearance
- Some anti-retrovirals (eg, nelfinavir increases clearance of both isomers)
- R-isomer metabolized by CYP2C19
- S-isomer metabolized by CYP2B6
- CYP3A4, 1A2, and 2D6

TOXIC EFFECTS

- Tolerance develops, but is lost after cessation of dosing
- Dose MUST be incremented, a standard dose to a naïve or an individual who has lost tolerance is potentially fatal
- Particular risk of fatality in children
- Respiratory depression
- Vasodilation with hypotension

MONITORING THERAPY

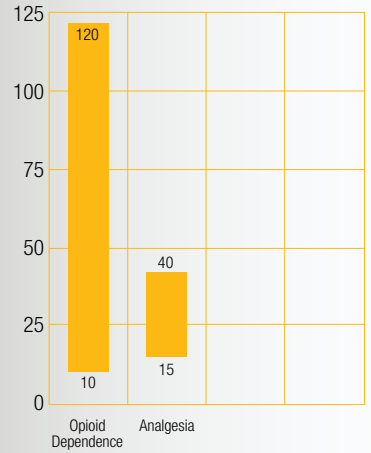
- There is a threshold of serum concentrations above which to avoid withdrawal symptoms and a higher value above which side effects become undesirable
- No benefit in monitoring isomeric forms
- Routine practice in urine monitoring is to detect the EDDP, (2-ethylidene-1,5-dimethyl-3,3-diphenyl-pyrrolidine) metabolite as a marker of adherence to therapy

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	~4 h
Route of elimination	Hepatic metabolism (~25% excreted renally)
Elimination half-life	15-40 h (R-isomer ~37 h, S-isomer ~28 h)
Time to steady state	4-8 days of chronic dosing
Protein binding	~90%
Target range	150-250 µg/L (430-720 nmol/L) for opioid dependence

TYPICAL ADULT DOSES (mg/d)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Analgesics

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

- Acetaminophen
- Acetylsalicylic Acid

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

ACETAMINOPHEN [PARACETAMOL] (Tylenol®, non-proprietary)

CLINICAL USE

- Analgesic
- Anti-pyretic

USUAL DOSE AND DOSE INTERVAL

- Five hundred milligrams to 1000 mg every 4-6 hours to a maximum of 4000 mg/d
- Child: age-dependent, conform to local practice

FACTORS AFFECTING CONCENTRATION

- CYP1A2 and 2E1

TOXIC EFFECTS

- Hepatic damage in overdose (may not be apparent until 4-6 days after overdose)
- Other side effects (eg, rash rare)

MONITORING THERAPY

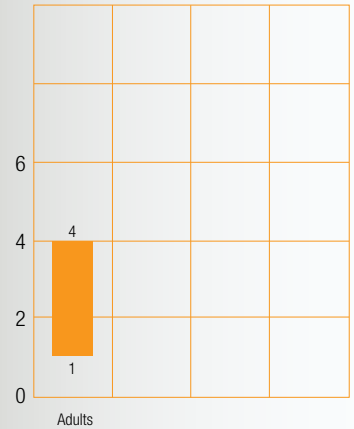
- There is no need to monitor therapy, measurements in overdose predict the probability of hepatotoxicity and guide the decision to administer antidote therapy

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	0.5-1.0 h
Route of elimination	Hepatic metabolism (~3% excreted renally)
Elimination half-life	1-4 h (shorter in children)
Time to steady state	5-20 h of chronic dosing
Protein binding	20%-30%
Target range	Serum concentrations should be related to an hepatic damage nomogram accepted in your country

TYPICAL ADULT DOSES (mg/d)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

ACETYLSALICYLIC ACID [ASPIRIN]

CLINICAL USE

- Analgesic
- Anti-inflammatory
- Anti-platelet (prophylaxis of cerebrovascular disease and acute coronary syndromes)

USUAL DOSE AND DOSE INTERVAL

- Analgesia/anti-inflammatory: 300-900 mg every 4-6 hours as necessary to a maximum of 4000 mg/day
- Anti-platelet: 300 mg dispersed or chewed-on presentation with a myocardial ischemic event, then 75 mg/day as prophylaxis
- Avoid use in children (risk of Reye's syndrome)

FACTORS AFFECTING CONCENTRATION

- pH-dependent gastric absorption
- Metabolized to salicylic acid then to salicyl acyl glucuronide and other compounds
- Renal excretion pH dependent (more rapid at alkaline pH)
- Hypoalbuminemia (decreased binding)

TOXIC EFFECTS

- Gastric irritation, contraindicated if previous ulcer
- Increased bleeding times
- Hypersensitivity reactions
- Tinnitus, vertigo
- Bronchospasm
- Hepatic and renal damage following overdose
- HLA-DRB*1302-DQB1*0609-DPB*0201 associated with urticaria

MONITORING THERAPY

- Now no longer advised as a non-steroidal anti-inflammatory
- Monitoring is only necessary in chronic anti-inflammatory dosing
- Concentration measurements aid treatment in overdose

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	1-2 h (preparation dependent)
Route of elimination	Hepatic metabolism (~10% excreted renally)
Elimination half-life	(salicylic acid) 3 h (single dose); ~ 20 h (chronic dosing)
Time to steady state	5-7 days of chronic dosing
Protein binding	~50%-90% (concentration dependent)
Target range	150-300 mg/L (1.1-2.2 mmol/L) (anti-inflammatory, less for analgesia)

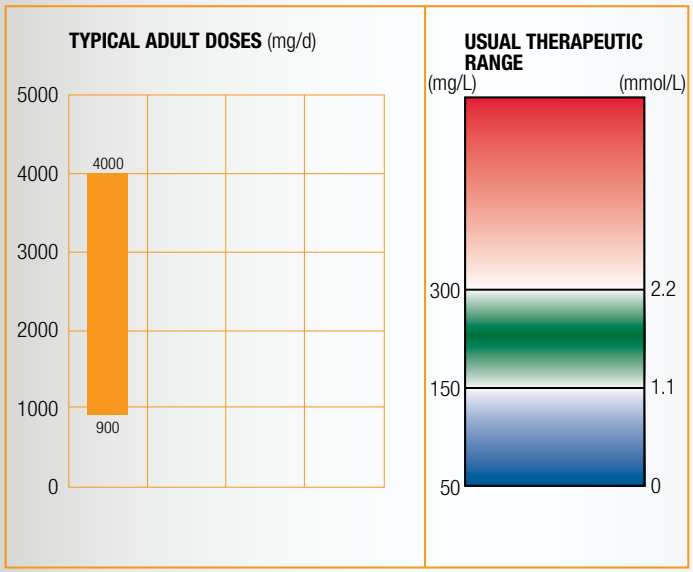


Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Antibiotics

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

AMINOGLYCOSIDES

- Amikacin
- Gentamicin
- Tobramycin

OTHER ANTIBIOTICS

- Teicoplanin
- Vancomycin

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

AMIKACIN

CLINICAL USE

- Broad spectrum antibiotic active against some Gram-positive and many Gram-negative organisms
- Used in treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli
- More resistant than gentamicin to enzyme inactivation
- Active against *Pseudomonas aeruginosa*

USUAL DOSE AND DOSE INTERVAL

- By IM injection, slow IV injection or infusion: 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses in severe infection.
  Max 1.5 g daily for up to 10 days
- Recent practice is to use once-daily dosing; amikacin is dosed at a level ~4 times greater than gentamicin at 20-28 mg/kg
- Child: 15 mg/kg daily in 2 divided doses

FACTORS AFFECTING CONCENTRATION

- Large, highly polar molecule
- Very poor oral bioavailability – must be given parenterally
- Not metabolized, excreted renally
- Short plasma half-life (2-3 h) unless renal function impaired
- Terminal half-life very long and drug may accumulate if therapy continued for > 7-10 days

TOXIC EFFECTS

- Vestibular and auditory damage (often irreversible) related to degree of exposure
- Nephrotoxicity (reduces excretion and may precipitate vicious cycle)
- May impair neuromuscular transmission – avoid in myasthenia gravis

MONITORING THERAPY

- Use of aminoglycosides is a delicate balance between achieving concentrations necessary for effect and avoiding toxicity
- Monitoring is essential to achieve effective therapy, especially in patients with renal impairment

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Peak (only used on divided-dose regimes): 1 h post-dose (30-60 min after infusion complete) Trough: Immediately before next dose
Time to peak	1 h
Route of elimination	> 90% excreted renally
Elimination half-life	2-3 h with normal renal function
Time to steady state	10-15 h with normal renal function
Protein binding	< 10%
Target range	Trough: < 10 mg/L On once-daily dosing, target is a trough concentration of < 5 mg/L Peak: 20-30 mg/L. Once daily/extended-dose regimes – seek local advice

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

GENTAMICIN

CLINICAL USE

- Broad spectrum antibiotic active against some Gram-positive and many Gram-negative organisms
- Used in treatment of serious infections sometimes with a penicillin or metronidazole (or both)
- Used in combination with other antibiotics in endocarditis
- Active against *Pseudomonas aeruginosa*

USUAL DOSE AND DOSE INTERVAL

- By IM injection, slow IV injection or infusion
- Once-daily/extended dosing interval regimes
- Once-daily 5-7 mg/kg, then adjust according to serum gentamicin concentration
- Multiple-dose regimes, 3-5 mg/kg daily (in divided doses every 8 h) Child: 6 mg/kg daily (2 mg/kg every 8 h)
- Endocarditis (with other antibacterials) 1 mg/kg every 8 h

FACTORS AFFECTING CONCENTRATION

- Large, highly polar molecule
- Very poor oral bioavailability – must be given parenterally
- Not metabolized, excreted renally
- Short plasma half-life (2-3 h) unless renal function impaired
- Terminal half-life very long and drug may accumulate if therapy continued for > 7-10 days

TOXIC EFFECTS

- Vestibular and auditory damage (often irreversible)
- Nephrotoxicity (reduces excretion and may precipitate vicious cycle)
- May impair neuromuscular transmission – avoid in myasthenia gravis

MONITORING THERAPY

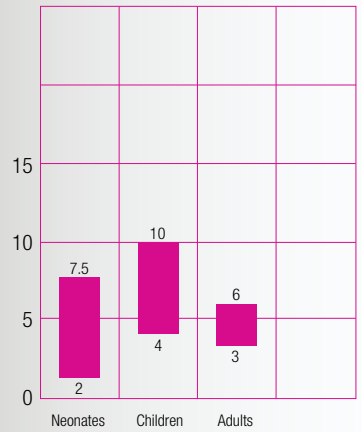
- Extended dosing interval regimes give higher peak and lower trough concentrations and have superseded multiple-dose regimes in many patients with normal renal function
- Guidelines on concentration monitoring for these regimes should be sought locally
- Use of aminoglycosides is a delicate balance between achieving concentrations necessary for effect and avoiding toxicity
- Monitoring is essential to achieve effective therapy, especially in patients with renal impairment

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Peak: 1 h post-dose (30-60 min after infusion complete)
Time to peak	1 h
Route of elimination	> 90% excreted renally
Elimination half-life	2-3 h with normal renal function
Time to steady state	10-15 h with normal renal function
Protein binding	< 10%
Target range	Once-daily/extended dose regimes: Seek local advice for specific regime Multiple dose regimes: Trough: < 2 mg/L (< 1 in endocarditis) Peak: 5-10 mg/L (3-5 in endocarditis)

USUAL DOSAGE (mg/kg/d maintenance)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

TOBRAMYCIN

CLINICAL USE

- Broad-spectrum antibiotic active against some Gram-positive and many Gram-negative organisms
- Used in treatment of serious infections sometimes with a penicillin or metronidazole (or both)
- Slightly more active against *Pseudomonas aeruginosa* than gentamicin
- May be given by nebulizer in chronic *Ps. aeruginosa* infection in cystic fibrosis

USUAL DOSE AND DOSE INTERVAL

- By IM injection, slow IV injection or infusion
- Three mg/kg daily (in divided doses every 8 h)
- Once-daily in severe infection up to 5 mg/kg daily in divided doses every 6-8, reduced to 3 mg/kg daily as soon as clinically indicated
- Child: 2-2.5 mg/kg every 8 h
- Endocarditis (with other antibacterials) 1 mg/kg every 8 h

FACTORS AFFECTING CONCENTRATION

- Large, highly polar molecule
- Very poor oral bioavailability – must be given parenterally
- Not metabolized, excreted renally
- Short plasma half-life (2-3 h) unless renal function impaired
- Terminal half-life very long and drug may accumulate if therapy continued for > 7-10 days

TOXIC EFFECTS

- Vestibular and auditory damage (often irreversible)
- Nephrotoxicity (reduces excretion and may precipitate vicious cycle)
- May impair neuromuscular transmission – avoid in myasthenia gravis

MONITORING THERAPY

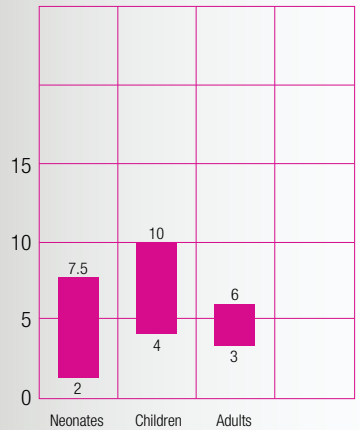
- Use of aminoglycosides is a delicate balance between achieving concentrations necessary for effect and avoiding toxicity
- Monitoring is essential to achieve effective therapy, especially in patients with renal impairment

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Peak: 1 h post-dose (30-60 min after infusion complete) Trough: Immediately before next dose
Time to peak	1 h
Route of elimination	> 90% excreted renally
Elimination half-life	2-3 h with normal renal function
Time to steady state	10-15 h with normal renal function
Protein binding	< 10%
Target range	Once-daily/extended-dose regimes: Seek local advice for specific regime Multiple-dose regimes: Trough: < 2 mg/L (< 1 in endocarditis) Peak: 5-10 mg/L (3-5 in endocarditis)

USUAL DOSAGE (mg/kg/d maintenance)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

TEICOPLANIN

CLINICAL USE

- Glycopeptide antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive bacilli including multiresistant staphylococci (MRSA)
- Used in prophylaxis and treatment of endocarditis and other serious infections caused by Gram-positive cocci
- Also used (added to dialysis fluid) in treatment of dialysis-associated peritonitis
- Very similar to vancomycin, but has a longer duration of action allowing once-daily administration

USUAL DOSE AND DOSE INTERVAL

- By IV injection or infusion:
  Initially 400 mg every 12 h for 3 doses, subsequently 200 mg once daily (400 mg once daily for severe infections). Higher doses may be needed in patients over 85 kg, or in severe burns or MRSA infection
  Streptococcal endocarditis: initially 6 mg/kg every 12 h for 3 doses, then 6 mg/kg once daily
  Enterococcal endocarditis: initially 10 mg/kg every 12 h for 3 doses, then 10 mg/kg once daily
  Child: By intravenous injection or infusion:
  Initially 10 mg/kg every 12 h for 3 doses, subsequently 6 mg/kg once daily
  (10 mg/kg once daily for severe infections or in neutropenia)

FACTORS AFFECTING CONCENTRATION

- Large, highly polar molecule
- Very poor oral bioavailability – must be given parenterally
- Not metabolized, excreted renally
- Long terminal half-life (> 100 h)

TOXIC EFFECTS

- Hypersensitivity reactions
- Transient increase in serum creatinine, renal failure
- Mild hearing loss and vestibular damage reported
- Rarely, flushing reactions with infusion

MONITORING THERAPY

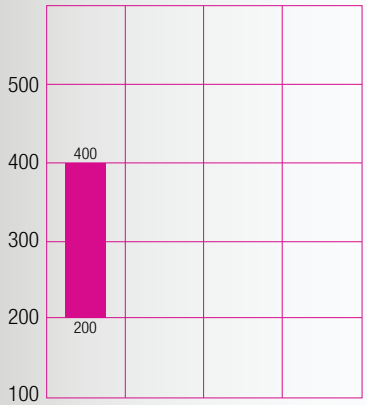
- No relationship between plasma concentration and toxicity has been established and teicoplanin is not monitored routinely
- Plasma concentrations may help to optimize therapy in some patients

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

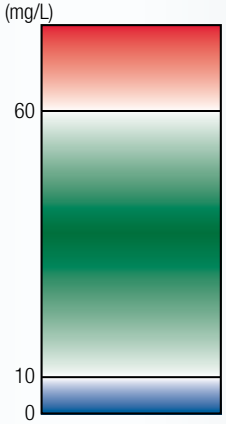
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough: Immediately before next dose
Time to peak	N/A
Route of elimination	97% excreted renally
Elimination half-life (terminal)	100-150 h
Time to steady state	14 days or more
Protein binding	> 90%
Target range	Trough: 10-60 mg/L (15-60 mg/L in endocarditis, 20-60 mg/L for *Staphylococcus aureus)*

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

VANCOMYCIN

CLINICAL USE

- Glycopeptide antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive bacilli including multiresistant staphylococci (MRSA)
- Used in prophylaxis and treatment of endocarditis and other serious infections caused by Gram-positive cocci
- Also used (added to dialysis fluid) in treatment of dialysis-associated peritonitis
- Oral administration restricted to treatment of antibiotic-associated colitis in severely ill patients

USUAL DOSE AND DOSE INTERVAL

- By intravenous infusion:
  1-1.5 g every 12 h (over 65 years, 500 mg every 12 h or 1 g once daily)
  Child: 15 mg/kg every 8 h, max 2 g daily

FACTORS AFFECTING CONCENTRATION

- Large, highly polar molecule
- Very poor oral bioavailability – must be given parenterally except in pseudomembranous colitis
- Not metabolized, excreted renally
- Short plasma half-life (4-6 h) unless renal function impaired

TOXIC EFFECTS

- Vestibular and auditory damage
- Nephrotoxicity (reduces excretion and may precipitate vicious cycle)
- Risk of toxicity enhanced if aminoglycosides given concurrently
- Flushing of the upper body ("red man" syndrome) occurs if infusion too rapid or too high a plasma concentration is attained

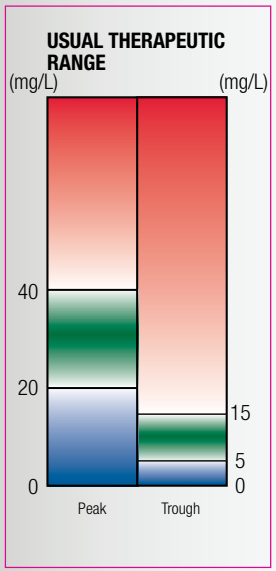
MONITORING THERAPY

- Indications for monitoring have been controversial, but there is definitely a role for monitoring in achieving maximum effect with minimum toxicity
- Some workers advocate monitoring in all patients treated for > 48 h, others restrict monitoring to subgroups of high-risk patients with renal impairment or those receiving other nephrotoxic drugs, children and pregnant women

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Peak: 1 h post-dose (30-60 min after infusion complete) Trough: Immediately before next dose
Time to peak	1 h
Route of elimination	80% excreted renally
Elimination half-life	4-7 h with normal renal function (longer in the elderly)
Time to steady state	20-35 h with normal renal function
Protein binding	< 10%
Target range	Trough: 5-15 mg/L (3-7 µmol/L) Peak: 20-40 mg/L (14-28 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Antiepileptics

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

CARBAMAZEPINE

CLINICAL USE

- Partial and secondary generalized tonic-clonic seizures
- Primary generalized tonic-clonic seizures
- Prophylaxis of bipolar affective disorder, mania and as a mood stabilizer
- Effective for pain relief in trigeminal neuralgia

USUAL DOSE AND DOSE INTERVAL

- Epilepsy: initially 100-200 mg 1-2 times daily, increasing to 0.4-1.2 g daily in divided doses (lower doses in children also age-dependent, lower initial dose in elderly). Up to 2 g may be needed
- Prophylaxis of bipolar disorder: usually 400-600 mg daily in divided doses, max 1.6 g daily
- Trigeminal neuralgia: initially 100 mg 1-2 times daily, increasing to 200 mg 3-4 times daily in divided doses, max 1.6 g daily

FACTORS AFFECTING CONCENTRATION

- Metabolized to the epoxide, then to the diol by CYP3A4 and CYP2C8
- Liver disease reduces clearance
- Increased clearance in children and pregnancy, reduced in old age
- Induces its own metabolism – half-life falls after 1-3 weeks' administration
- Metabolism induced by phenytoin and phenobarbitone
- Metabolism inhibited by valproate and lamotrigine

TOXIC EFFECTS

- Dose-limiting side effects: blurred vision, nystagmus, dizziness, ataxia, headache, nausea, vomiting
- Erythematous rash in 3%-5% of patients
- Syndrome of inappropriate antidiuresis may occur (hyponatraemia, water overload)
- Rarely leucopenia
- Patients need to be warned of the risk of blood, hepatic and skin disorders
- HLA-B*1502 associated with Stevens-Johnson syndrome

MONITORING THERAPY

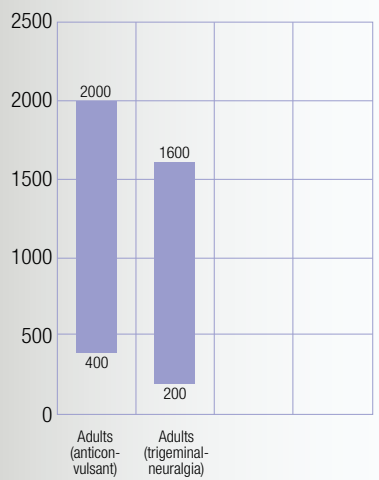
- Relationship between plasma concentration and effect complicated by active metabolites (CBZ-epoxide)
- Some patients may be controlled at concentrations < 4 mg/L or require concentrations >12 mg/L
- Monitoring essential when seizure control is difficult to attain, but some patients can be managed effectively with minimal monitoring
- Blood count, renal and hepatic monitoring needed

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

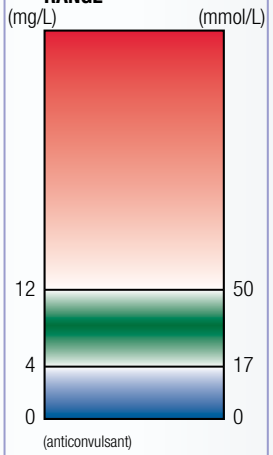
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Pre-dose (trough sample)
Time to peak	4-8 h (longer with sustained release forms)
Route of elimination	Hepatic metabolism (< 1% excreted renally)
Elimination half-life	10-20 h (shorter in children or in patients on enzyme-inducing drugs)
Time to steady state	2-6 days of chronic dosing
Protein binding	~75%
Target range	4-12 mg/L (17-50 mmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

ETHOSUXIMIDE

CLINICAL USE

- Used in typical or atypical absence seizures
- Rarely used in tonic-clonic seizures

USUAL DOSE AND DOSE INTERVAL

- Adults and children over 6 yrs: initially 500 mg daily increased by 250 mg at intervals of 4-7 days to usual dose of 1-1.5 g (max 2 g) daily
- Child up to 6 years: initially 250 mg daily, increased gradually to usual dose of 20 mg/kg daily, max 1 g daily

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP3A4 to inactive hydroxyl metabolite
- Low protein binding
- Chiral drug, used clinically as racemate

TOXIC EFFECTS

- Gastrointestinal – nausea, vomiting, anorexia
- CNS – dizziness, lethargy, sedation (tolerance develops)
- Hiccup
- Blood disorders

MONITORING THERAPY

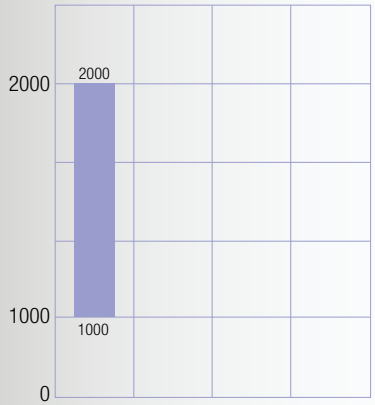
- Monitoring rarely necessary
- Long half-life requires slow-dosage changes
- Synergistic pharmacodynamic interaction with valproate in some cases

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

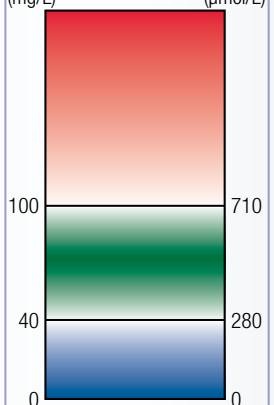
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Pre-dose (trough sample)
Time to peak	2-4 h (adults) 3-7 h (children)
Route of elimination	Hepatic metabolism (20% excreted renally)
Elimination half-life	40-60 h
Time to steady state	5-15 days of chronic dosing
Protein binding	< 5%
Target range	40-100 µg/L (280-710 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

FELBAMATE

CLINICAL USE

- Adjunctive therapy for partial seizures
- Used in Lennox-Gastaut syndrome

USUAL DOSE AND DOSE INTERVAL

- Six hundred milligrams bid orally

FACTORS AFFECTING CONCENTRATION

- Fifty percent excreted unchanged
- Metabolized by CYP3A4 and CYP2E1
- Metabolites include: 2-hydroxy; parahydroxy; and the monocarbamate
- Clearance increased by phenytoin and carbamazepine

TOXIC EFFECTS

- Risk of serious toxicity: aplastic anemia and hepatic failure
- Atropaldehyde, a reactive metabolite, may cause the aplastic anemia
- Common side effects include: anorexia, weight loss, vomiting, insomnia, nausea, headache, dizziness, and somnolence
- Toxicity limits use to difficult-to-control epilepsy

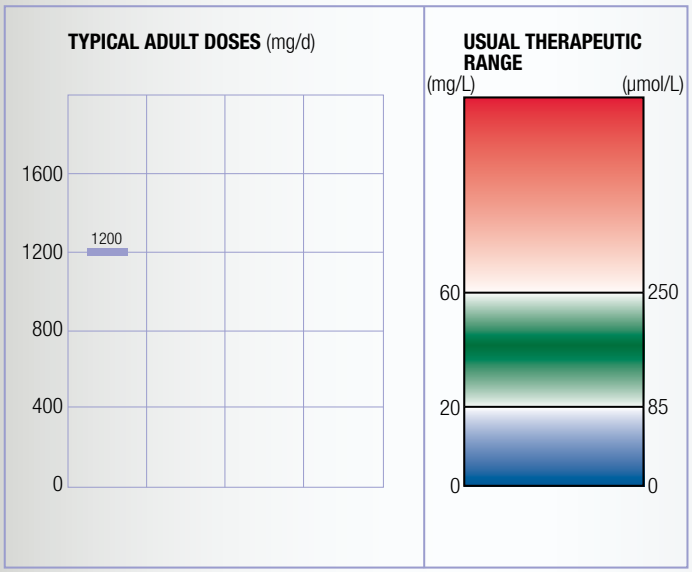
MONITORING THERAPY

- Monitor liver function tests and full blood counts at least monthly
- Felbamate increases phenytoin, phenobarbitone and valproate concentrations
- Felbamate decreases carbamazepine concentrations

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	1-4 h
Route of elimination	50% renal
Elimination half-life	~ 20 h
Time to steady state	~ 6 days of chronic dosing
Protein binding	~25%
Target range	20-60 mg/L (85-250 umol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

GABAPENTIN

CLINICAL USE

- Used in partial seizures with or without secondary generalization
- Neuropathic pain
- Trigeminal neuralgia

USUAL DOSE AND DOSE INTERVAL

- Epilepsy: 100 mg-300 mg tid: (increase in 300 mg/day increments according to response to max 3.6 g/day in 3 divided doses)

FACTORS AFFECTING CONCENTRATION

- Renally excreted – accumulates in renal failure

TOXIC EFFECTS

- Mild side-effects; typically fatigue, somnolence, ataxia, and dizziness
- Weight gain on chronic therapy
- Avoid abrupt withdrawal

MONITORING THERAPY

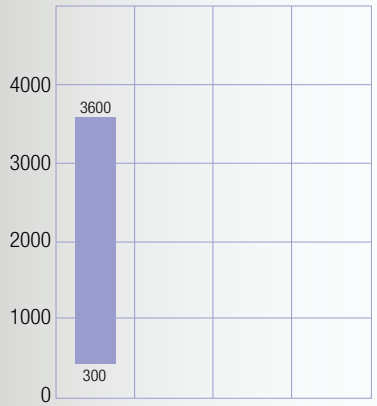
- Unnecessary

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

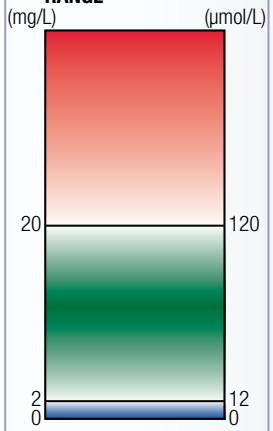
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	2-3 h
Route of elimination	Renal (100%)
Elimination half-life	5-7 h
Time to steady state	~2 days of chronic dosing
Protein binding	< 3%
Target range	2-20 mg/L (12-120 µmol/L) suggested

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

LAMOTRIGINE

CLINICAL USE

- Effective first-line anticonvulsant
- Partial and generalized tonic-clonic seizures
- Use alone or in combination with other anticonvulsants
- Also used in treatment of bipolar disorder in some countries

USUAL DOSE AND DOSE INTERVAL

- Monotherapy: 25 mg once daily for 2 weeks, then 50 mg o.d. for 2 weeks, then increase by max 50-100 mg o.d. to normal maintenance dose of 100-200 mg daily in 1-2 divided doses
- Adjunctive therapy: with valproate or oxcarbazepine: as for monotherapywith enzyme inducers: double above dosing rates to a maximum of 400 mg per day. Check local practice

FACTORS AFFECTING CONCENTRATION

- Phenytoin, carbamazepine, and phenobarbitone induce metabolism
- Valproate decreases clearance
- Lamotrigine inhibits carbamazepine epoxide formation
- Metabolized by hepatic glucuronidation
- Clearance increased in the first trimester of pregnancy and in patients on oral contraception

TOXIC EFFECTS

- Three percent to 5% of patients suffer rash as a side effect. Gradual introduction reduces the incidence of rash
- Neurological side-effects (eg, weakness, visual disturbance, dizziness)
- Gastrointestinal disturbances
- Combination with other anticonvulsants can precipitate multi-organ failure, status epilepticus and disseminated intravascular coagulation

MONITORING THERAPY

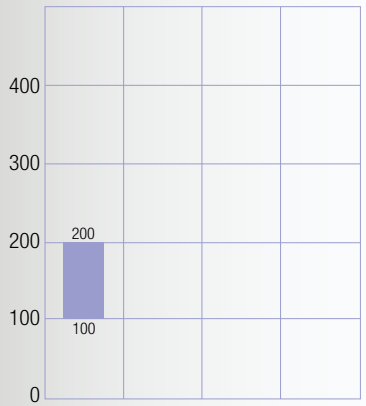
- Plasma concentration reflects effect
- Target range: up to 24 mg/L (94 µmol/L) when used as single therapy
- Toxicity occurs in 5% above 15 mg/L (59 µmol/L) rising to 15% above 20 mg/L (78 µmol/L)
- Interactions with other anticonvulsants mean measurement of concentrations is helpful in designing a dosing regimen

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

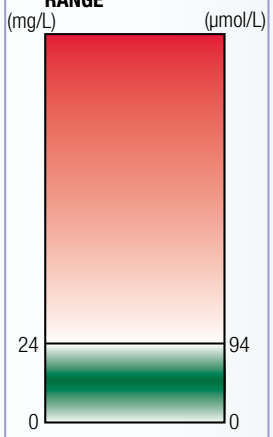
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	~3 h
Route of elimination	Hepatic metabolism (~10% excreted renally)
Elimination half-life	20-35 h (shorter in children). Approx. 15 h when given with enzyme inducers. Approx. 60 h when given with valproate
Time to steady state	5-7 days of chronic dosing
Protein binding	~60%
Target range	< 24 mg/L (< 94 umol/L) (see *Monitoring Therapy* on p. 60)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

LEVETIRACETAM

CLINICAL USE

- Monotherapy or adjunctive therapy of partial seizures with or without secondary generalization

USUAL DOSE AND DOSE INTERVAL

- Adult doses (check local guidance for children)
- Monotherapy: 250 mg twice daily initially, increased by 250 mg twice daily every 2 weeks to a maximum of 1.5 g twice daily
- Adjunctive therapy: 500 mg twice daily initially, increased by 500 mg twice daily every 2-4 weeks to a maximum of 1.5 g twice daily

FACTORS AFFECTING CONCENTRATION

- Approximately 65% excreted renally as unchanged drug
- Approximately 25% following hydroxylation of the acetamide group
- Not metabolized by cytochrome enzymes, so not induced or inhibited by drugs metabolized by these enzymes
- Renal excretion means decreased clearance when renal function impaired
- Stereoselective

TOXIC EFFECTS

- Good safety profile
- Principal side-effects are asthenia, dizziness and somnolence
- Wide range of more severe side-effects occur rarely

MONITORING THERAPY

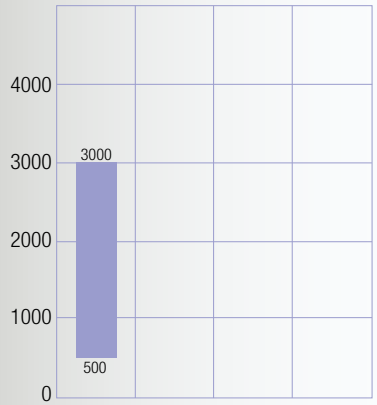
- No evidence to justify routine monitoring
- Target range of 6-20 mg/L [35-118 µmol/L] has been suggested

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

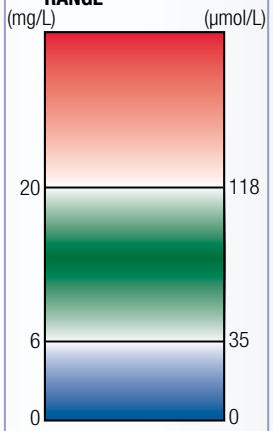
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	0.5-1.0 h
Route of elimination	Renal elimination of ~65% unchanged drug
Elimination half-life	6-8 h
Time to steady state	~2 days of chronic dosing
Protein binding	< 10%
Target range	6-20 mg/L (35-118 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

OXCARBAZEPINE

CLINICAL USE

- Monotherapy and adjunctive therapy of partial seizures with or without secondary generalization
- Pain relief in trigeminal neuralgia

USUAL DOSE AND DOSE INTERVAL

- Three hundred milligrams twice daily initially, increasing in steps of up to 600 mg daily at weekly intervals
- Typical doses 600-2400 mg daily in divided doses
- Children [6-18y]: initially 8-10 mg/kg daily increasing weekly by similar doses to a maximum of 46 mg/kg in divided doses
- Trigeminal neuralgia: dosing not definitively established

FACTORS AFFECTING CONCENTRATION

- Extensive reductive metabolism to the 10-hydroxy metabolite by cytosolic arylketone reductase
- The 10-hydroxy metabolite is pharmacologically active
- Rapid first-pass metabolism means oxcarbazepine is effectively a pro-drug for the 10-hydroxy metabolite
- Minimal cytochrome enzyme metabolism of oxcarbazepine means inductive/inhibitory drugs do not affect its pharmacokinetics
- Kinetics much less variable than carbamazepine

TOXIC EFFECTS

- Similar neurological side-effect profile to carbamazepine
- High incidence (~25%) of hyponatraemia (< 125 mmol/L)
- Patients need to be warned of the risk of blood, hepatic and skin disorders
- Less liver damage than with carbamazepine

MONITORING THERAPY

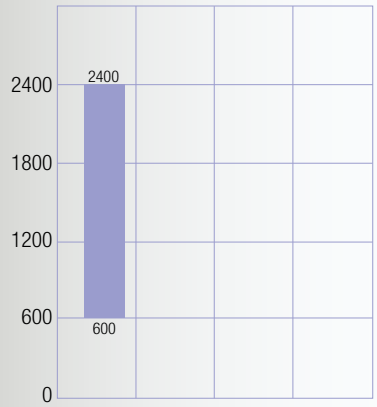
- Monitoring of oxcarbazepine and/or its metabolite is not established practice; a tentative range for the latter of 12-24 mg/L [48-95 µmol/L] has been suggested

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

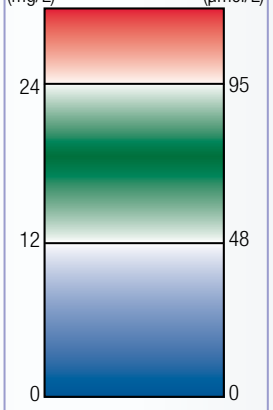
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	1-3 h (hydroxy metabolite peaks ~2-6 h)
Route of elimination	Hepatic metabolism (hydroxy metabolite undergoes phase one and 2 hepatic metabolism and some renal excretion)
Elimination half-life	~2 h (hydroxy metabolite: 8-16 h)
Time to steady state	2-7 days of chronic dosing for hydroxy metabolite
Protein binding	~60% (~50% for the hydroxy metabolite)
Target range	12-24 mg/L [48-95 µmol/L] has been suggested for 10-hydroxy metabolite

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE FOR THE 10-HYDROXY METABOLITE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

PHENOBARBITAL/PRIMIDONE

CLINICAL USE

- All forms of epilepsy except absence seizures
- Phenobarbital used as second-line treatment in status epilepticus
- Primidone is a pro-drug for phenobarbital; it is rarely used
- Previously widely used, phenobarbital is now used infrequently

USUAL DOSE AND DOSE INTERVAL

- Phenobarbital: 60-180 mg at night; 5-8 mg/kg for children
- Primidone: 125 mg at night, increasing by 125 mg every 3 days to 500 mg in 2 divided doses; increase by increments of 250 mg every 3 days to a maximum of 1500 mg in divided doses

FACTORS AFFECTING CONCENTRATION

- Phenobarbital induces its own metabolism
- Phenytoin and valproate decrease clearance
- Renal impairment decreases clearance
- Renal excretion is pH sensitive, alkalinity increases clearance
- CYP2C9 and CYP2C19

TOXIC EFFECTS

- Sedation is a common early side effect, tolerance develops
- Hyperkinesia and behavioral disturbances in children
- Nystagmus and ataxia
- Megaloblastic anemia (1%-2%)
- Osteomalacia
- Avoid in porphyria
- Rash occurs in 1%-2% of patients

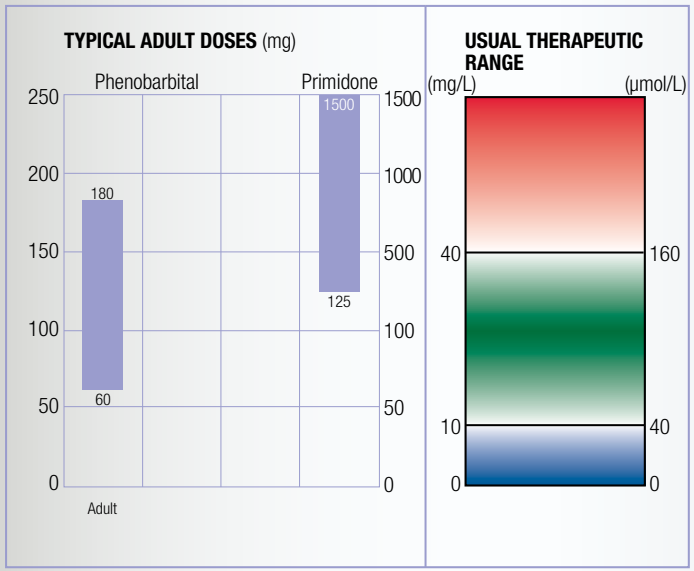
MONITORING THERAPY

- Tolerance occurs
- Poor correlation between drug concentration and effect
- Target range must be interpreted flexibly
- Very low phenobarbital concentrations may have a significant anticonvulsant effect and withdrawal may provoke breakthrough seizures

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Not important at steady state (as long as half-life and dosage frequency causes minimal concentration variation between doses)
Time to peak	2-4 h (see *Optimum sampling time* above)
Route of elimination	~70% hepatic metabolism (~30% excreted renally)
Elimination half-life	80-120 h (shorter following metabolic induction)
Time to steady state	17-25 days of chronic dosing; however, metabolic induction will require dose changes and the establishment of a new steady-state
Protein binding	~50%
Target range	10-40 mg/L (40-160 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

PHENYTOIN/FOSPHENYTOIN

CLINICAL USE

- Widely used alone and in combination with other anticonvulsants
- All forms of epilepsy except absence seizures
- Fosphenytoin, a phenytoin pro-drug, for IV use in status epilepticus
- Used to treat trigeminal neuralgia if carbamazepine inappropriate

USUAL DOSE AND DOSE INTERVAL

- One hundred fifty to 300 milligrams per day initially, adjust according to response and plasma concentration, usual dose 200-500 mg daily
- Child initially 5 mg/kg in 2 divided doses to a maximum of 8 mg/kg
- Fosphenytoin is equivalent to phenytoin in a weight ratio of 3:2. Doses are stated in phenytoin equivalents (PE) (eg, 1.5 mg fosphenytoin = 1.0 mg PE)
- Fosphenytoin (status epilepticus) 20 mg (PE)/kg initially, then 50-100 mg (PE)/minute; maintenance 4-5 mg (PE)/kg daily in 1 or 2 divided doses with trough plasma concentration monitoring. Consult local guidance for children

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP2C9 [90%] and 2C19 [10%], limited capacity
- Saturation kinetics (nonlinear or zero-order kinetics) – ie, small changes in dose may lead to disproportionate changes in plasma phenytoin concentrations
- Individuals vary as to when their kinetics become nonlinear
- Valproate displaces protein-bound phenytoin
- Variable and slow absorption rate
- Unbound (ie, free phenytoin concentrations) affected by some drugs or changes in availability of albumin for binding
- Pregnancy increases clearance
- Induces metabolism of some other antiepileptics and many other drugs
- CYP2C8

TOXIC EFFECTS

- Poor side-effect profile limits use
- Neurotoxicity (nystagmus, dysarthria, diplopia, ataxia)
- Chronic side-effects may cause disabling or disfiguring (eg, ataxia or gingival hyperplasia, acne and hirsutism)
- Rare severe reactions (eg, megaloblastic anemia)
- Paradoxical seizures if dose too high

MONITORING THERAPY

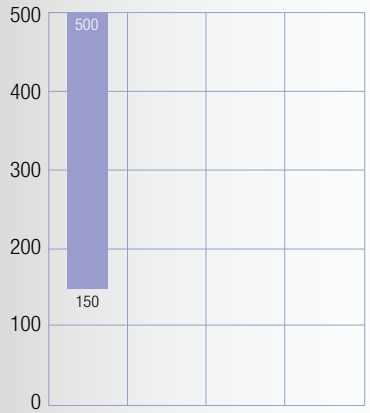
- Essential to monitor therapy to enable informed and safe-dosage changes
- There is no dose-effect relationship
- Saliva concentrations reflect plasma concentrations
- Free plasma concentrations best reflect effect
- Dose changes should be made judiciously
- Be aware of drug interactions

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

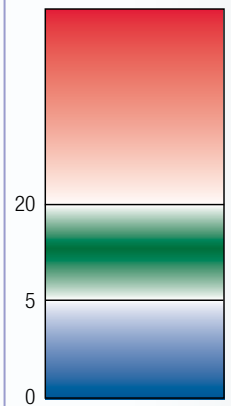
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	In steady-state this is not too important as the effective half-life is long, a trough sample if on short-term fosphenytoin
Time to peak	3-12 h (formulation dependent)
Route of elimination	Hepatic metabolism (> 95%)
Apparent elimination half-life	6-24 h (up to 60 h if metabolism saturated)
Time to steady state	2-6 days of chronic dosing
Protein binding	~92%
Target range	Total phenytoin: 5-20 mg/L (20-80 µmol/L) Free phenytoin: 0.5-2.0 mg/L (2-8 µmol/L) V_{MAX}: 100-1000mg/d Km: 1-15mg/L (4-60 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE (mg/L)



Adults, children, infants > 30 months

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

TOPIRAMATE

CLINICAL USE

- Monotherapy or adjunctive therapy for generalized, tonic-clonic or partial seizures
- Adjunctive therapy for seizures in Lennox-Gastaut syndrome
- Migraine prophylaxis

USUAL DOSE AND DOSE INTERVAL

- Monotherapy: 25 mg at night for a week, then increments of 25-50 mg/day over 1-2 weeks taken in 2 divided doses to a maximum of 400 mg. Child over 6 years: 0.5-1.0 mg/kg at night, initial increasing by 0.5-1.0 mg/kg/d at intervals of 1-2 weeks to a maximum of 15 mg/kg/d in 2 divided doses
- Adjunctive therapy: as for monotherapy, but a maximum dose of 800 mg/d. Child: 25 mg at night for 1 week incrementing by 1-3 mg/kg/d over 1-2 weeks in 2 divided doses to a maximum of 15 mg/kg/d

FACTORS AFFECTING CONCENTRATION

- Excreted renally – clearance reduced in renal impairment
- Increased clearance if given with carbamazepine or felbamate

TOXIC EFFECTS

- Risk of acute myopia with secondary angle-closure glaucoma, typically within a month of starting therapy; raised intraocular pressure (monitor)
- Need adequate hydration to avoid nephrolithiasis as makes urine alkaline favoring calcium phosphate stones
- Avoid in porphyria

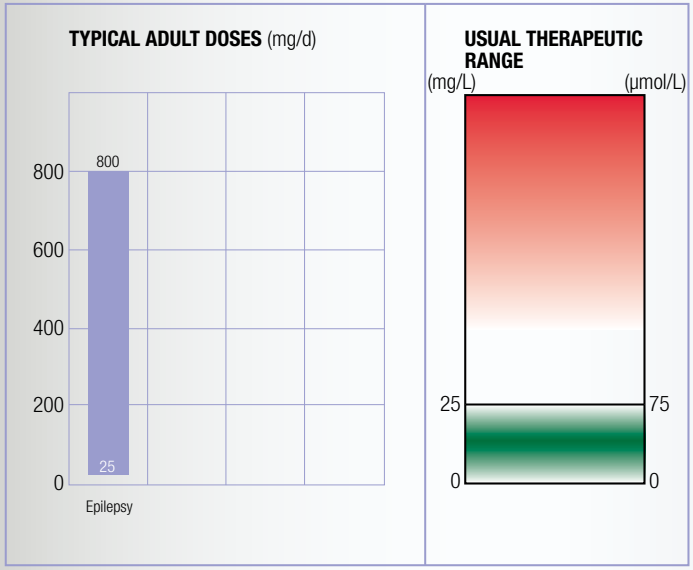
MONITORING THERAPY

- Side effects worsen above 25 mg/L
- Usefulness of monitoring has not been established

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	1-2.5 h
Route of elimination	~90% excreted renally
Elimination half-life	20-30 h
Time to steady state	5-7 days of chronic dosing
Protein binding	~15%
Target range	< 25 mg/L (< 75 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

VALPROATE

CLINICAL USE

- All forms of epilepsy
- Drug of choice in primary generalized epilepsy, generalized absences and myoclonic seizures
- Acute mania associated with bipolar disorder

USUAL DOSE AND DOSE INTERVAL

- Six hundred milligrams per day in 2 doses after food, increasing by 200 mg/d every 3 days to a maximum of 2500 mg/d; usual dose 1000-2000 mg/d
- Child under 12 years, if over 20 kg, 400 mg/d in divided doses initially to a maximum of 35 mg/kg/d
- Mania (as semisodium valproate [Depakote]) initially 750 mg/day in 2-3 divided doses increased according to response. Usual dose as above

FACTORS AFFECTING CONCENTRATION

- Complex pharmacokinetic profile
- Clearance increased by carbamazepine, phenytoin and phenobarbital
- Protein-binding is concentration-dependent and also displacement by endogenous metabolites (eg, free fatty acids; affected by hypoalbuminemia)
- Wide concentration variation across the dosage interval
- Active metabolites which are eliminated much more slowly than parent drug

TOXIC EFFECTS

- Weight gain common
- Nausea, vomiting (reduced with enteric-coated forms)
- Teratogenic (association with open spina bifida)
- Hyperammonemia
- Thrombocytopenia
- Increased transaminases in first few months of therapy
- Risk of severe/fatal hepatic toxicity in children under 2 years
- Pancreatitis

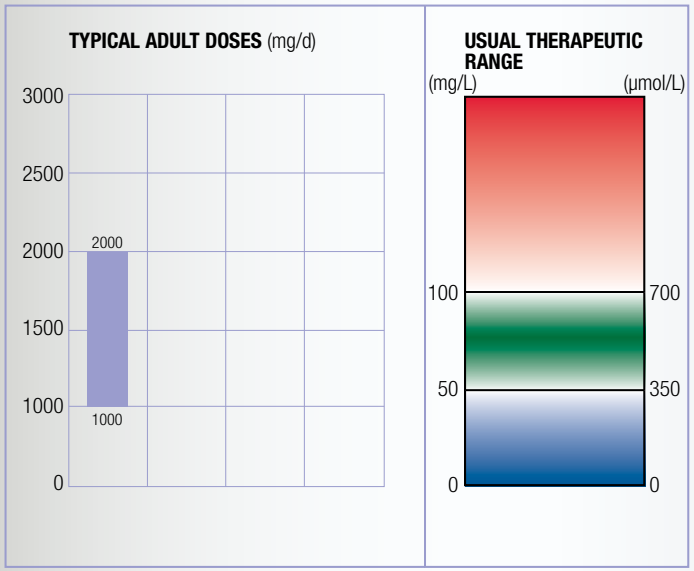
MONITORING THERAPY

- Monitor full blood count and liver function
- The evidence is AGAINST monitoring plasma concentrations in either epileptic or bipolar disorder patients as there is wide intra-individual variation in concentrations with no relationship to therapeutic effect; also toxicity may be related to longer half-life metabolites

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	1-4 h (longer with enteric-coated forms: 3-8 h)
Route of elimination	~95% hepatic metabolism
Elimination half-life	11-17 h
Time to steady state	3-7 days of chronic dosing
Protein binding	~95% (concentration dependent, decreasing binding above) ~ 80 mg/L (320 µmol/L; also affected by endogenous metabolites)
Target range	There is little evidence for the 50-100 mg/L (350-700 µmol/L) range often cited, or the range of 50-125 mg/L (350-870 µmol/L) cited for bipolar disorder monitoring. Plasma concentrations show poor correlation with effect.



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

VIGABATRIN

CLINICAL USE

- Specialist-initiated adjunctive therapy where other anticonvulsants have failed
- Monotherapy for infantile spasms (West's syndrome)

USUAL DOSE AND DOSE INTERVAL

- One thousand milligrams initially increased by 500 mg increments at weekly intervals to a maximum of 3000 mg/d in 1 or 2 divided doses. Children: seek local advice
- Infantile spasms: 50 mg/kg/d adjust according to response over a week to a maximum of 150 mg/kg/d

FACTORS AFFECTING CONCENTRATION

- Supplied as a racemate, though only the S(+) isomer has pharmacological activity
- Excreted renally – clearance reduced in renal impairment

TOXIC EFFECTS

- Irreversible visual-field defects
- Neurological (eg, drowsiness, stupor, impaired concentration, slow-wave EEG)

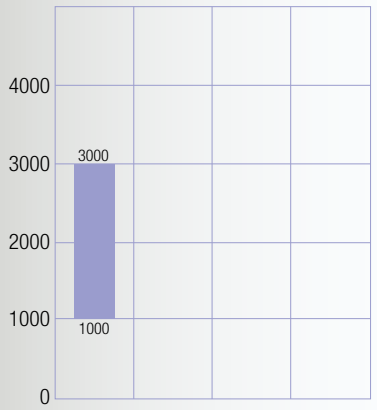
MONITORING THERAPY

- Irreversible enzyme inhibitor – long pharmacodynamic half-life
- There is no evidence plasma concentration monitoring is necessary. Any measurement would need to be of the S(+) isomer

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS	
Optimum sampling time	Before a dose (trough sample)
Time to peak	0.5-2.0 h
Route of elimination	~70% excreted renally
Elimination half-life	6-8 h — S(+), active isomer elimination age independent, the R(-) inactive isomer clearance increases as children mature.
Time to steady state	4 days of chronic dosing (clinical effects of changing dose take 2-10 days to be fully manifest)
Protein binding	~0%
Target range	No evidence for monitoring

TYPICAL ADULT DOSES (mg/d)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

ZONISAMIDE

CLINICAL USE

- Adjunctive therapy for refractory partial seizures

USUAL DOSE AND DOSE INTERVAL

- Fifty miligrams per day in 2 divided doses increasing weekly thereafter as required by 100 mg/d in 2 divided doses to a maximum of 500 mg/d in 2 divided doses

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP3A4
- Clearance increased by enzyme-inducing drugs
- Lamotrigine may inhibit clearance
- Saturable binding of zonisamide to red cells (maximized before therapeutically effective concentrations are reached)
- NAT2 (N-acetyl transferase)

TOXIC EFFECTS

- Sensitivity to sulphonamides (zonisamide is a sulphonamide derivative)
- Nephrolithiasis (incidence ~1%)
- Weight loss

MONITORING THERAPY

- Evidence for toxicity being associated with concentrations over 40 mg/L (190 µmol/L)
- Interaction with other anticonvulsants and the long half-life make monitoring helpful in deciding dosing

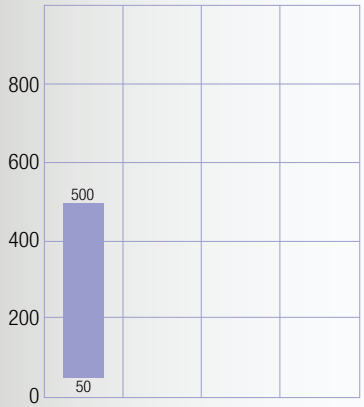
This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Antiepileptics

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Long half-life makes sampling time less critical in steady-state (however, sampling at trough is advised)
Time to peak	< 2 h
Route of elimination	~70% hepatic metabolism (remainder excreted renally)
Elimination half-life	~65 h (50% less if taken with enzyme-inducing drugs)
Time to steady state	~ 2 weeks of chronic dosing
Protein binding	~40%
Target range	10-20 mg/L (47-94 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE

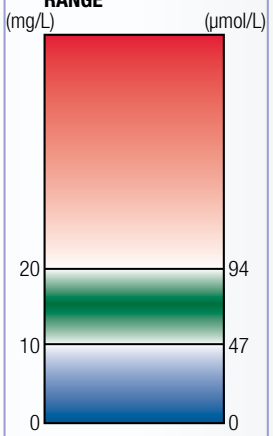


Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Antineoplastics

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

METHOTREXATE

CLINICAL USE

- As part of combined anti-cancer drug regimens
- Psoriasis
- Crohn's disease
- Rheumatoid arthritis and other autoimmune diseases

USUAL DOSE AND DOSE INTERVAL

- Dosing in anticancer regimens varies depending on the protocol
- Crohn's disease: intramuscular injection of 25 mg to induce remission, then 15 mg weekly maintenance
- Rheumatoid arthritis:
  - Moderate to severe: orally 7.5 mg weekly, adjusted according to response to a maximum of 20 mg weekly
  - Severe: subcutaneous, intramuscular or intravenously 7.5 mg weekly, increased by 2.5 mg weekly to a maximum of 25 mg weekly
- Psoriasis: oral, intramuscular or intravenously 10-25 mg weekly, adjusted according to response

FACTORS AFFECTING CONCENTRATION

- Triphasic elimination – distribution, renal elimination, elimination from intracellular distribution
- Polyglutamate metabolites accumulate intracellularly

TOXIC EFFECTS

- Kills rapidly-dividing cells (eg, bone marrow: degree related to dose)
- Nephrotoxic in high doses
- Reversible hepatotoxicity (monitor procollagen III peptide)
- Cirrhosis on chronic low dosing

MONITORING THERAPY

- In high dose (ie, anti-cancer therapy) there is a need to determine whether leucovorin (calcium folinate) rescue is necessary
- In low dose, monitor white cell counts and hepatorenal function – methotrexate concentration monitoring unnecessary

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	As required by protocol, often 24, 48 and (if necessary) 72 h post high-dose therapy
Time to peak	~ 1.0 h for low-dose oral therapy
Route of elimination	~Predominantly renal excretion, ~90% in high-dose regimes
Elimination half-life	5-9 h (less if urine alkalinized)
Time to steady state	1-2 days of chronic low dosing
Protein binding	~50%
Target range	< 1 µmol/L (< 450 ug/L) 48 h post high-dose therapy or according to protocol. (The convention is to use molar SI rather than mass SI units for methotrexate concentrations.)

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Bronchodilator, Analeptic

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

- Theophylline
- Caffeine

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

THEOPHYLLINE

CLINICAL USE

- Relaxes smooth muscle and relieves/prevents bronchoconstriction
- Used in asthma/stable chronic obstructive pulmonary disease
- No longer a first- or second-line drug in chronic asthma but still useful in patients who have difficulty with inhalers and those with predominantly nocturnal symptoms

USUAL DOSE AND DOSE INTERVAL

- Modified release preparations
- 200-500 mg every 12 h
- Children 2-6 years 60-120 mg every 12 h
- Children 6-12 years 125-250 mg every 12 h
- Rate of absorption from modified-release preparations can vary between brands – Be aware when switching brands
- NB aminophylline preparations are the EDTA salt of theophylline and are approx. 80% theophylline by weight

FACTORS AFFECTING CONCENTRATION

- Metabolized to 1,3 dimethyluric acid in the liver
- Rate of metabolism affected by many factors – hepatic disease, other drugs, dietary factors, smoking
- Concentrations increased in heart failure, cirrhosis and viral infections and by erythromycin, cimetidine, ciprofloxacin
- Concentrations decreased in smokers, chronic alcoholics and by drugs that induce hepatic metabolism (eg, phenytoin, carbamazepine, rifampicin)
- CYP1AZ and CYP2E1

TOXIC EFFECTS

- Side effects relatively frequent
- Mild/moderate effects (nausea, headache, jitteriness) are common within the target range
- More serious effects (tremor, agitation, insomnia, diarrhea, palpitations, tachycardia, cardiac arrhythmias, seizures, cardiorespiratory arrest) occur with increasing frequency at plasma concentrations above 20 mg/L (110 µmol/L)

MONITORING THERAPY

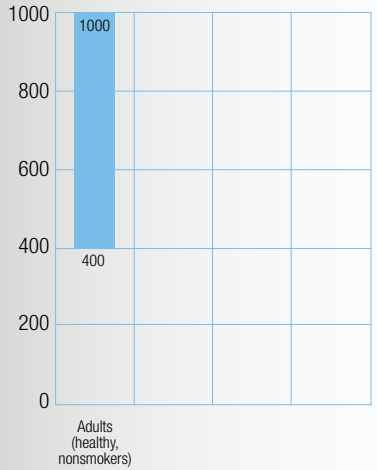
- Poor correlation between dose and plasma concentration due to variation in rate of metabolism
- Monitoring useful in initial dosage optimization and in confirming toxicity and monitoring overdose

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

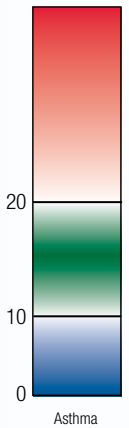
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough: immediately before next dose Peak: 4-8 h post-dose (modified release preparations) 2 h post-dose (rapid-release)
Time to peak	1-2 h post-dose (rapid-release) 4-8 h post-dose (modified release)
Route of elimination	Hepatic metabolism (< 20% renally)
Elimination half-life	3-9 h
Time to steady state	2-3 days (oral dosing, adults)
Protein binding	50%-65%
Target range	10-20 mg/L (55-110 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE (mg/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

CAFFEINE

CLINICAL USE

- Stimulates CNS, relaxes smooth muscle and relieves/prevents bronchoconstriction
- Used in neonates to treat apnea of prematurity (in preference to theophylline as dose regimes are similar and effects are more predictable)

USUAL DOSE AND DOSE INTERVAL

- (Premature neonates, as caffeine citrate): Loading 20 mg/kg, maintenance 5 mg/kg/day given once daily by intravenous infusion

FACTORS AFFECTING CONCENTRATION

- Metabolized in liver in adults
- Elimination prolonged in neonates due to immaturity of cytochrome P450 1A2
- Parent drug is predominantly excreted renally in the first 3 months of life

TOXIC EFFECTS

- CNS effects – restlessness, tremor, seizures
- Cardiovascular – tachycardia and fibrillation
- Produces much less tachycardia and fewer fits than theophylline

MONITORING THERAPY

- The much lower toxicity and more predictable pharmacokinetics of caffeine compared to theophylline combine to make therapeutic monitoring unnecessary. May be useful in cases of inadequate response on standard dose regimes or in confirming toxicity

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Immediately before next dose
Time to peak	Rapid on IV
Route of elimination	Renal (in neonates)
Elimination half-life	72-96 h (range 40-230 h) (neonates)
Time to steady state	N/A
Protein binding	30%-40%
Target range	5-20 mg/L (25-100 µmol/L) (in neonatal apnea)

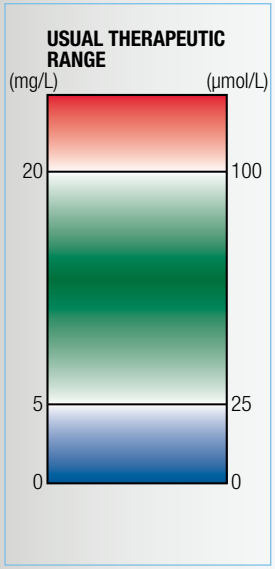


Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Cardiac Agents

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

ANTI-ARRHYTHMICS

- Amiodarone
- Disopyramide
- Flecainide
- Lidocaine
- Procainamide/Napa

CARDIAC GLYCOSIDES

- Digitoxin
- Digoxin

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

AMIODARONE

CLINICAL USE

- Treatment of cardiac arrhythmias when other drugs are ineffective or contraindicated
- May be used for all types of tachyarrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias and ventricular fibrillation, atrial flutter and fibrillation and tachyarrhythmias associated with Wolff-Parkinson-White syndrome
- Treatment should be initiated and monitored under hospital or specialist supervision

USUAL DOSE AND DOSE INTERVAL

- Oral: 200 mg 3 times daily for 1 week reducing to 200 mg twice daily for a further week. Maintenance – 200 mg once daily or the minimum needed to control arrhythmia
- IV via central venous catheter: 5 mg/kg over 20-120 min with ECG monitoring, then according to response. Max 1.2 g in 24 h

FACTORS AFFECTING CONCENTRATION

- Very large volume of distribution – when given orally, takes days to suppress ventricular tachycardias. Loading dose required
- IV administration has immediate effect
- Very long elimination half-life
- Extensively metabolized on first pass through liver to mono-N-desethylamiodarone (active, and even more lipid-soluble)
- Inhibits metabolism of warfarin, digoxin and simvastatin by inhibition of cytochrome P450 3A4 pathways – a range of other drugs are affected
- Metabolism of amiodarone affected by inhibitors of metabolism such as cimetidine and grapefruit juice

TOXIC EFFECTS

- Toxicity related to dosage and duration of treatment
- Pulmonary toxicity is the most serious adverse effect (cough, dyspnea, respiratory distress)
- Thyroid abnormalities in around 10% of patients on long-term treatment (hypothyroidism 2-4x more common than hyperthyroidism). Check thyroid function every 6 months
- Photosensitivity and corneal deposits common
- Cardiac toxicity and hepatotoxicity rare

MONITORING THERAPY

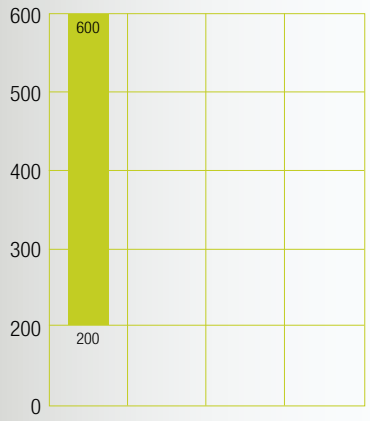
- Most patients do not need monitoring; if monitoring is performed there is no additional benefit in measuring the desethyl metabolite
- Monitoring in some patients may help differentiate treatment failure from poor adherence or suboptimal dosing

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

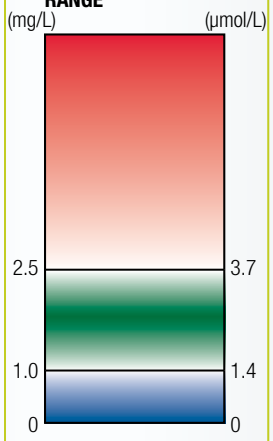
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (immediately before next dose)
Time to peak	5 h
Route of elimination	Hepatic metabolism
Elimination half-life	50 days
Time to steady state	Months
Protein binding	> 98%
Target range	1.0-2.5 mg/L (1.4-3.7 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DISOPYRAMIDE

CLINICAL USE

- To control supraventricular and ventricular arrhythmias after myocardial infarction (by intravenous injection) – but impairs cardiac contractility
- Oral administration limited by antimuscarinic effect – caution in prostatic enlargement and susceptibility to open-angle glaucoma

USUAL DOSE AND DOSE INTERVAL

- Oral: 300-800 mg daily in divided doses
- By slow IV injection with ECG monitoring: 2 mg/kg over at least 5 min to max 150 mg followed immediately by: 200 mg orally, then 200 mg every 8 h for 24 h, or 400 mcg/kg/h IV infusion, max 300 mg in first hour and 800 mg/day

FACTORS AFFECTING CONCENTRATION

- Predominantly renal excretion
- Some hepatic metabolism to active metabolite which has approx. 25% activity of parent compound
- Phenytoin and other hepatic-inducing agents increase disopyramide clearance
- Commercially available disopyramide is a racemic mixture. The S(+) isomer has about twice the pharmacological effect of the R(-) isomer, and is more strongly bound to protein

TOXIC EFFECTS

- Gastrointestinal (nausea, vomiting, diarrhea)
- Cardiovascular (decreased cardiac output, conduction disturbances)
- Anticholinergic – dry mouth, blurred vision, urinary retention

MONITORING THERAPY

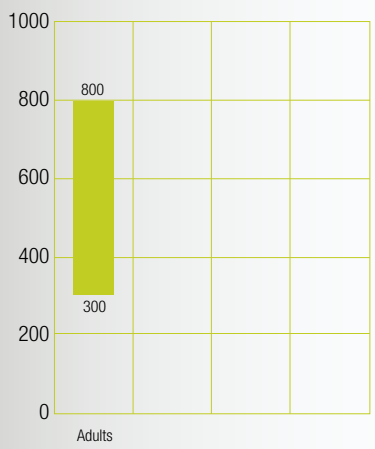
- Monitoring complicated by variable protein binding – free disopyramide concentrations are recommended (concentration range 0.5-2.0 mg/L)
- Monitoring helpful in ensuring efficacy and avoiding toxicity, especially in patients with renal impairment
- Measurement of individual stereoisomers may be useful

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

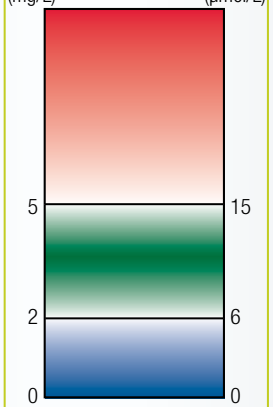
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (immediately before next dose)
Time to peak	2-3 h
Route of elimination	35%-60% excreted renally Hepatic metabolism to active metabolite
Elimination half-life	4.5-9 h with normal renal function
Time to steady state	1-2 days with normal renal function
Protein binding	30%-65% (concentration dependent)
Target range	2-5 mg/L (6-15 µmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

FLECAINIDE

CLINICAL USE

- To control serious symptomatic ventricular arrhythmias, junctional re-entry tachycardia and paroxysmal atrial fibrillation

USUAL DOSE AND DOSE INTERVAL

- Oral: (under hospital supervision) ventricular arrhythmias, initially 100 mg twice daily (max 400 mg daily), reduced after 3-5 days if possible. Supraventricular arrhythmias 50 mg twice daily, increased if required to max 300 mg daily. By slow IV injection: (in hospital with ECG monitoring) 2 mg/kg over 30 min max 150 mg followed if required by infusion at 1.5 mg/kg/h for 1 h, reducing to 100-250 mcg/kg/h for up to 24 h, max 600 mg in first 24 h, then transfer to oral as above

FACTORS AFFECTING CONCENTRATION

- CYP2D6 substrate – shortened half-life in extensive metabolizers
- Clearance reduced in renal failure and heart failure

TOXIC EFFECTS

- Dizziness, visual disturbances, nausea, headache
- Cardiovascular – pro-arrhythmia, cardiac failure
- (On chronic therapy) – hypersensitivity, systemic lupus erythematosus, agranulocytosis

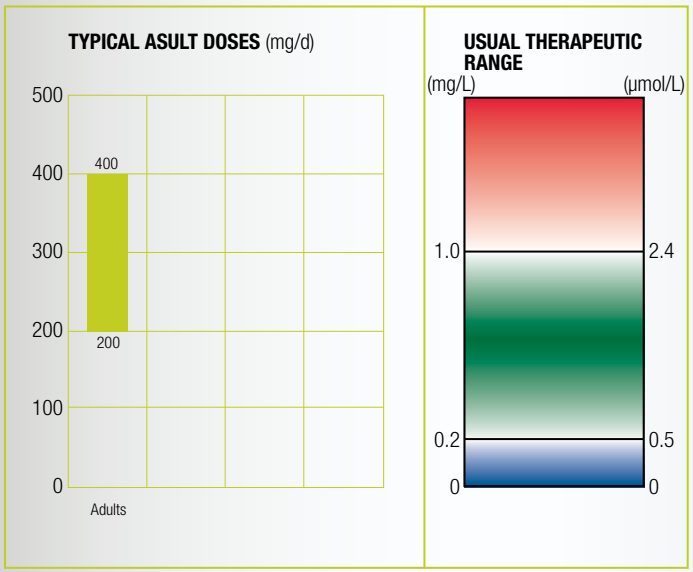
MONITORING THERAPY

- Most patients respond at plasma concentrations 0.2-0.6 mg/L

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (immediately before next dose)
Time to peak	2-3 h
Route of elimination	40%-45% excreted renally Hepatic metabolism (CYP 450 2D6)
Elimination half-life	8-14 h
Time to steady state	4-5 days
Protein binding	40%
Target range	0.2-1.0 mg/L (0.5-2.4 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

LIDOCAINE

CLINICAL USE

- To control ventricular arrhythmias after myocardial infarction (MI)
- Effective in suppressing ventricular tachycardia and reducing the risk of ventricular fibrillation following MI
- Also used as a local anaesthetic

USUAL DOSE AND DOSE INTERVAL

- By IV injection: 100 mg bolus over a few minutes (50 mg in lighter patients or those with severely impaired circulation) followed by infusion of 4 mg/min for 30 min, 2 mg/min for 2 h then 1 mg/min for up to 24 h; ECG monitoring required

FACTORS AFFECTING CONCENTRATION

- Predominantly hepatic metabolism to active metabolites (monoethylglycine xylidide and glycine xylidide)
- Volume of distribution decreased in congestive heart failure and dosage requirements are lower
- CYP1A2 and CYP3A

TOXIC EFFECTS

- CNS (drowsiness, dizziness, slurred speech, paraesthesiae, agitation). Hearing disturbances, disorientation, muscle twitching, convulsions and respiratory arrest at higher doses
- Cardiovascular: may depress myocardial contractility in high doses or cause hypotension, bradycardia and cardiac arrest

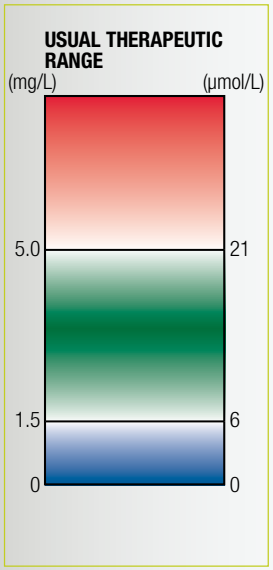
MONITORING THERAPY

- Monitoring may be helpful in ensuring efficacy and avoiding toxicity, especially in patients with circulatory impairment or liver disease

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	2 h after start of therapy with loading dose
Time to peak	NA
Route of elimination	Hepatic metabolism to active metabolite (< 10% excreted renally)
Elimination half-life	1-2 h
Time to steady state	8-10 h (less with loading dose)
Protein binding	60%-80% (α1-acid glycoprotein)
Target range	1.5-5 mg/L (6-21 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

PROCAINAMIDE

CLINICAL USE

- To control ventricular arrhythmias after myocardial infarction and atrial tachycardia

USUAL DOSE AND DOSE INTERVAL

- By slow IV injection: 100 mg with ECG monitoring, rate not exceeding 50 mg/min, repeated at 5 min intervals until arrhythmia controlled, max 1 g
- By IV infusion: 500-600 mg over 25-30 min with ECG monitoring, followed by maintenance at 2-6 mg/min, then if necessary by oral anti-arrhythmic treatment starting 3-4 h after infusion

FACTORS AFFECTING CONCENTRATION

- Excreted renally
- Procainamide is metabolized in the liver to N-acetylprocainamide (NAPA), which is less potent but also active
- Pharmacogenetic variation in rate of metabolism (bimodal distribution – slow and fast acetylators)
- NAT2

TOXIC EFFECTS

- Gastrointestinal disturbances – nausea, vomiting
- Mild CNS effects – malaise, disorientation
- Cardiovascular – conduction delay, hypotension and ventricular arrhythmias
- (On chronic therapy) – hypersensitivity, systemic lupus

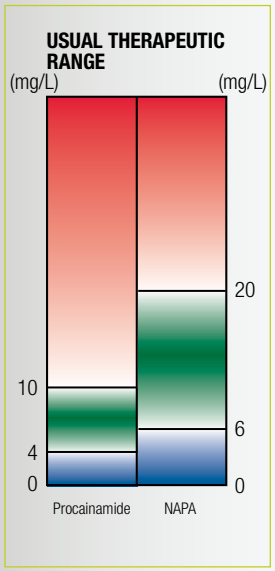
MONITORING THERAPY

- Metabolite NAPA may be present at higher concentrations than parent drug, and has longer elimination half-life. Both procainamide and NAPA concentrations should be measured

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	> 2 h after start of infusion
Time to peak	IV: 0.25-0.3 h
Route of elimination	60%-75% excreted renally Hepatic metabolism to active metabolite (NAPA)
Elimination half-life	2.5-5 h
Time to steady state	11-20 h
Protein binding	15%-20%
Target range	4-10 mg/L (17-43 µmol/L) NAPA: 6-20 mg/L (22-72 µmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DIGITOXIN

CLINICAL USE

- Structurally and functionally similar to digoxin, but used less frequently
- Increases the force of cardiac contraction and increases cardiac output
- Used in management of chronic cardiac failure where the dominant problem is systolic dysfunction
- Used in management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation

USUAL DOSE AND DOSE INTERVAL

- Maintenance: 100 mcg daily or on alternate days, may be increased to 200 mcg daily if necessary

FACTORS AFFECTING CONCENTRATION

- Digitoxin is not cleared renally, so useful in patients with concomitant heart failure and renal impairment
- Hepatic metabolism – one of the metabolites produced is cardioactive digoxin (minor pathway)
- Drug and metabolites are excreted into the gut via the bile and then reabsorbed (enterohepatic circulation) – this contributes to long half-life
- Hepatic disease has little effect as liver has considerable reserve capacity
- Antacids, cholestyramine and dietary fiber decrease absorption
- Enzyme inducers (eg, phenytoin and rifampicin) increase non-renal clearance

TOXIC EFFECTS

- Gastrointestinal: nausea, vomiting, diarrhea or constipation, abdominal pain
- Neurological: headache, fatigue, insomnia, confusion, vertigo
- Visual disturbances: blurred vision, color casts and colored halos are classic signs of cardiac glycoside toxicity
- Cardiac: bradycardia, atrioventricular block, ventricular tachycardias and other arrhythmias
- Toxicity is related to drug concentration but is exacerbated by hypokalemia (take care when diuretics are co-administered)
- Age and the severity of heart disease are also independent risk factors for the development of toxicity
- Severe toxicity can be treated with anti-digoxin antibodies (DigiBind). Use of DigiBind may invalidate immunoassays. Antidote has a lower affinity for digitoxin

MONITORING THERAPY

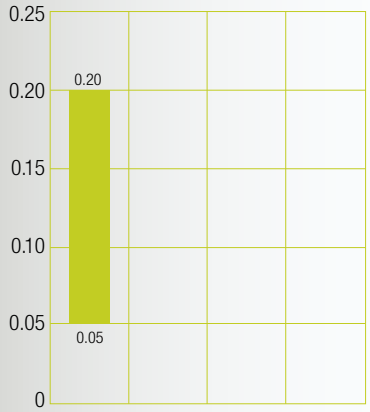
- Blood should be taken at least 6 h post-dose to allow distribution to occur and ensure plasma concentrations reflect tissue concentration
- Plasma digitoxin and plasma potassium should be measured
- Specific assays for digitoxin are not readily available, but it may react in some digoxin assays

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

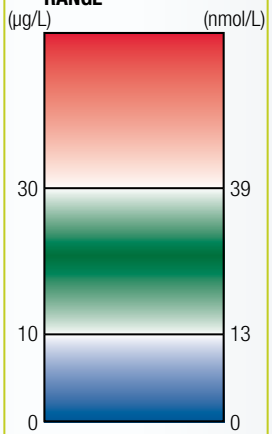
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (pre-dose) or > 6 h post-dose
Time to peak	3-6 h (oral, plasma)
Route of elimination	Hepatic metabolism 30% excreted renally
Elimination half-life	5-8 days
Time to steady state	Approx. 1 month
Protein binding	> 90%
Target range	10-30 µg/L (13-39 nmol/L)

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DIGOXIN

CLINICAL USE

- Increases the force of cardiac contraction and increases cardiac output
- Used in management of chronic cardiac failure where the dominant problem is systolic dysfunction
- Used in management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation

USUAL DOSE AND DOSE INTERVAL

- Atrial fibrillation and flutter: rapid digitalization: 0.75-1.5 mg orally over 24 h in divided doses. Maintenance: according to renal function and loading dose, 125-250 mcg daily
- Heart failure, for patients in sinus rhythm, 62.5-125 mcg once daily

FACTORS AFFECTING CONCENTRATION

- Renal elimination, so extra care needed in patients with impaired renal function and in the elderly
- Antacids, cholestyramine and dietary fiber decrease absorption
- Enzyme inducers (eg, phenytoin and rifampicin) increase nonrenal clearance
- Small changes in dose, may result in either loss of efficacy or serious adverse effects. Bioavailability may vary considerably between preparations, so care needed if changing preparation

TOXIC EFFECTS

- Gastrointestinal: nausea, vomiting, diarrhea or constipation, abdominal pain
- Neurological: headache, fatigue, insomnia, confusion, vertigo
- Visual disturbances: blurred vision, color casts and colored halos are classic signs of digoxin toxicity
- Cardiac: bradycardia, atrioventricular block, ventricular tachycardias and other arrhythmias
- Toxicity is related to drug concentration but is exacerbated by hypokalemia (take care when diuretics are co-administered)
- Age and the severity of heart disease are also independent risk factors for the development of toxicity
- Severe toxicity can be treated with anti-digoxin antibodies (DigiBind). Use of DigiBind may invalidate immunoassays

MONITORING THERAPY

- Blood should be taken at least 6 h post-dose to allow distribution to occur and ensure plasma concentrations reflect tissue concentration
- Plasma digoxin and plasma potassium should be measured
- Lower digoxin concentrations are now recommended in heart failure
- Endogenous substances may cross-react in digoxin immunoassays (digoxin-like immunoreactive substances, DLIS) and yield spuriously high results. More prevalent in the very young (particularly neonates) and the elderly. Commercial assays vary in their specificity for DLIS

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (pre-dose) or > 6 h post-dose
Time to peak	1 h (oral, plasma)
Route of elimination	60% excreted renally
Elimination half-life	36 h with normal renal function
Time to steady state	7-10 days
Protein binding	25%
Target range	0.8-2.0 µg/L (1.0-2.6 nmol/L) (in heart failure: 0.5-1.0 µg/L (0.6-1.3 nmol/L)

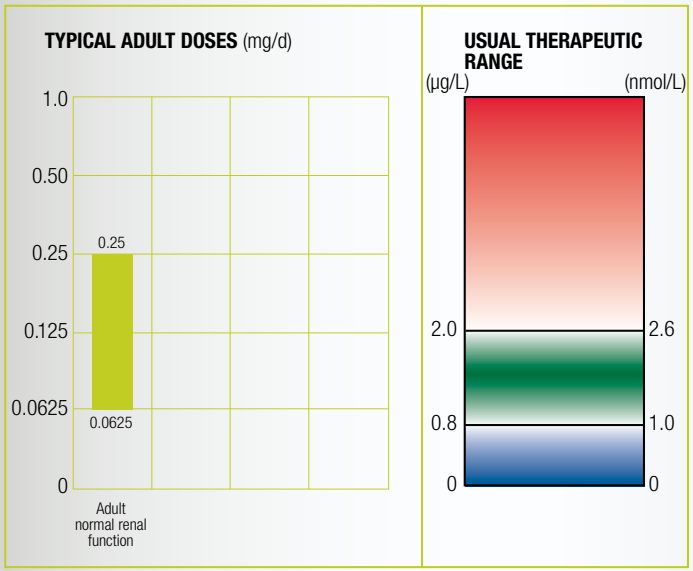


Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Immunosuppressive Agents

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

- Ciclosporin/Cyclosporine
- Mycophenolate
- Sirolimus
- Tacrolimus

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

CICLOSPORIN/CYCLOSPORINE

CLINICAL USE

- Transplantation: prevention of graft rejection following kidney, liver, heart, lung, heart-lung, bone marrow or pancreas transplants
- Treatment of transplant rejection in patients previously receiving other immunosuppressive agents
- Prophylaxis and treatment of graft-versus-host disease
- Nontransplant: treatment of severe psoriasis, atopic dermatitis, ulcerative colitis and rheumatoid arthritis when conventional therapy is ineffective or inappropriate
- Treatment of nephrotic syndrome
- Inhibits calcineurin phosphatase and limits T-cell activation

USUAL DOSE AND DOSE INTERVAL

- Following transplantation (oral) 10-15 mg/kg/day for 1-2 weeks post-operatively then reduced gradually to 2-6 mg/kg/day for maintenance in 2 divided doses
- Dose guided by blood cyclosporine concentration and renal function
- In dermatology 2.5 mg/kg/day in 2 divided doses increasing to 5 mg/kg/day if response not achieved, guided by renal function and blood cyclosporine concentration
- For nephrotic syndrome, initially 5 mg/kg/day in 2 divided doses, reduced according to efficacy to lowest effective level

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP3A enzyme system
- Substrate for P-glycoprotein transporter system
- No evidence that metabolites exhibit significant contribution to pharmacological effect
- Dosage adjustment needed in hepatic disease
- Widely varying pharmacokinetics between patients
- Highly lipophilic – accumulates in red cells
- Microemulsion formulation (neoral) has more reproducible absorption characteristics; sandimmun is administered intravenously
- Bioavailability varies between oral formulations – care needed when changing formulation

TOXIC EFFECTS

- Renal dysfunction is a serious adverse effect
- Raised blood pressure and hyperlipidemia
- Adverse cosmetic effects (gingival hyperplasia and hypertrichosis)
- Overimmunosuppression associated with infection and neoplasia

MONITORING THERAPY

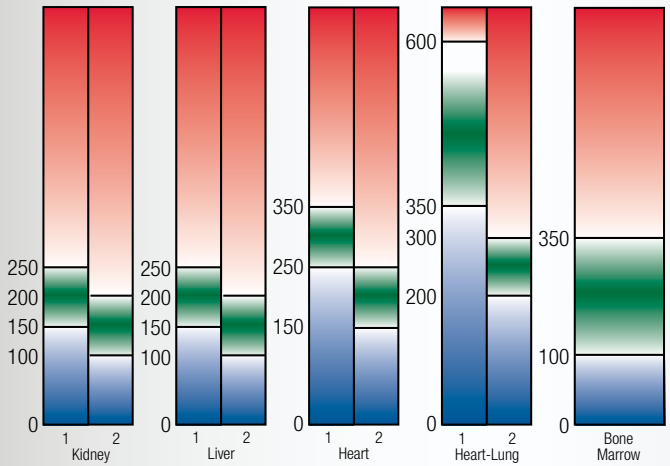
- Narrow therapeutic index and variable pharmacokinetics means that monitoring is essential for safe use of the drug
- Whole blood samples used (EDTA anticoagulant)
- Recommended sample times are trough or 2 h post-dose
- Target concentrations vary with time after transplantation, transplant type, other drugs, sample time and analytical method

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (C_0) or 2 h post dose (C_2) whole blood sample
Time to peak	1-6 h
Route of elimination	Hepatic metabolism < 1% excreted renally
Elimination half-life	12 h (range 4-53)
Time to steady state	2-6 days
Protein binding	> 98%
Target range	Varies widely with sample time transplant type and time after transplantation

EXAMPLE THERAPEUTIC RANGE (µg/L) **FOR TROUGH CYCLOSPORINE THERAPY**



1 = Induction therapy (approx. ≤ 3 months after transplantation); 2 = Maintenance therapy

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

MYCOPHENOLATE

CLINICAL USE

- Prevention of graft rejection following kidney, liver or heart transplants in combination with cyclosporine and corticosteroids
- Also widely used in combination with tacrolimus, sirolimus and everolimus
- Inhibits inosine monophosphate dehydrogenase and blocks lymphocyte proliferation

USUAL DOSE AND DOSE INTERVAL

- Cellcept (mycophenolate mofetil, MMF – the pro-drug): following kidney transplantation, starting dose (oral) 1 g twice daily. Following heart and liver transplantation, starting dose (oral) 1.5 g twice daily
- Myfortic (mycophenolate sodium, MPS) – following kidney transplantation, starting dose 720 mg twice daily
- 1 g mycophenolate mofetil is approximately equivalent to 720 mg mycophenolate sodium

FACTORS AFFECTING CONCENTRATION

- Rapidly absorbed from MMF formulation, prolonged absorption from MPS
- Mainly excreted renally
- Less than 10% hepatic metabolism to glucuronide, which is inactive and excreted into bile, then deglucuronidated and reabsorbed – a second absorption peak in MPA concentration may be observed
- Clearance decreases in the weeks following transplantation and MPA exposure per unit dose consequently increases
- Important interaction with cyclosporine – reduction in MPA exposure when administered with cyclosporine

TOXIC EFFECTS

- Gastrointestinal adverse effects (nausea, vomiting, diarrhea and abdominal pain) are common (less so with enteric-coated MPS)
- Increased incidence of leucopenia, anemia and thrombocytopenia
- Overimmunosuppression

MONITORING THERAPY

- Within-patient variability for pre-dose concentrations is high and isolated pre-dose measurements should be interpreted with caution
- Most monitoring experience is with the MMF formulation
- Plasma (EDTA anticoagulant) or serum samples used
- Sampling algorithms are available to estimate the total exposure (area under the drug concentration-time curve)
- Target concentrations (pre-dose, MMF formulation) approximately 1-2 mg/L are recommended following kidney transplantation, and 1-3 mg/L following heart transplantation
- AUC in the range 30-60 mg h/L recommended

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (pre-dose) or as needed to determine AUC by algorithm
Time to peak	1-2 h
Route of elimination	> 90% excreted renally
Elimination half-life	17 h
Time to steady state	NA
Protein binding	98%
Target range	Varies with transplant type, time of sample, method used and other medication (see *Optimum sampling time* above)

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

SIROLIMUS

CLINICAL USE

- Prevention of graft rejection in kidney transplant patients, initially in combination with cyclosporine and corticosteroids, then with corticosteroid only
- Inhibits T-cell proliferation by binding to protein kinase (mTOR) and blocking signal transduction

USUAL DOSE AND DOSE INTERVAL

- Loading dose of 6 mg then usual starting dose is 2 mg once daily in combination with cyclosporine and corticosteroid for 2-3 months; cyclosporine should then be withdrawn over 4-6 weeks, or sirolimus must be stopped
- Adjust dose according to sirolimus concentration
- Give sirolimus 4 h after cyclosporine

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP3A in the liver and gut to hydroxy- and demethyl-metabolites. No evidence that metabolites are active
- Substrate for P-glycoprotein
- When co-administered with the microemulsion formulation of cyclosporine, absorption of sirolimus is enhanced, almost doubling the effective dose (hence recommendation to give sirolimus 4 h after cyclosporine)
- Concentrated in red cells – whole blood samples used

TOXIC EFFECTS

- Hematological – anemia, leucopenia, thrombocytopenia
- Hypertriglyceridemia and hypercholesterolemia
- Lymphocele formation and impaired wound healing
- Not intrinsically nephrotoxic, but prolonged use with cyclosporine/tacrolimus has a synergistic effect on nephrotoxicity
- Overimmunosuppression associated with infection and neoplasia

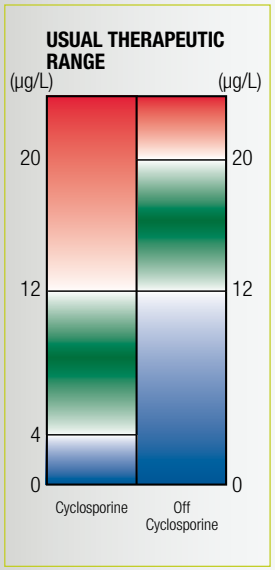
MONITORING THERAPY

- Dose is a poor predictor of drug exposure
- Monitoring is a regulatory requirement
- Particularly necessary in hepatic impairment, during treatment with inducers or inhibitors of metabolism and after discontinuing them
- Whole blood (EDTA anticoagulant) samples used

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (pre-dose) Whole blood sample
Time to peak	1-2 h
Route of elimination	Hepatic metabolism 1%-2% excreted renally
Elimination half-life	62 h
Time to steady state	5-7 days
Protein binding	92%
Target range	With cyclosporine: 4-12 µg/L (4.4-13.1 nmol/L) Off cyclosporine: 12-20 µg/L (13.1-21.9 nmol/L) (HPLC assay – results by immunoassay are higher)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

TACROLIMUS

CLINICAL USE

- Prevention of graft rejection in kidney, liver and heart transplant patients
- Treatment of graft rejection in patients resistant to treatment with other immunosuppressives
- Inhibits calcineurin phosphatase and limits T-cell activation
- Also used in moderate to severe atopic eczema (in the ointment formulation, protopic)

USUAL DOSE AND DOSE INTERVAL

- Vary with type of transplant and time post-transplant. Oral doses following kidney transplantation are of the order of 0.1-0.2 mg/kg/day in 2 divided doses (once-daily with modified release formulation, advagraf)

FACTORS AFFECTING CONCENTRATION

- Metabolized by CYP3A in the liver and gut. No evidence that metabolites are active
- Metabolism significantly affected by genetic polymorphism of CYP3A4/CYP3A5
- Substrate for P-glycoprotein
- Range of significant drug interactions involving induction/inhibition of CYP3A or P-glycoprotein
- Concentrated in red cells – whole blood samples used

TOXIC EFFECTS

- Hematological – anemia, leucopenia, thrombocytopenia
- Hypertriglyceridemia and hypercholesterolemia
- Lymphocele formation and impaired wound healing
- Not intrinsically nephrotoxic, but prolonged use with cyclosporine/tacrolimus has a synergistic effect on nephrotoxicity
- Overimmunosuppression associated with infection and neoplasia

MONITORING THERAPY

- Dose is a poor predictor of drug exposure
- Monitoring is a regulatory requirement
- Particularly necessary in hepatic impairment, during treatment with inducers or inhibitors of metabolism and after discontinuing them
- Whole blood (EDTA anticoagulant) samples used

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Trough (pre-dose) Whole blood sample
Time to peak	1-3 h
Route of elimination	Hepatic metabolism < 1% excreted renally
Elimination half-life	10-20 h
Time to steady state	2-5 days
Protein binding	> 98%
Target range	Varies with sample time transplant type and time after transplantation. Typically 15 µg/L (18.2 nmol/L) following kidney transplantation, reducing to 5-10 µg/L (6.1-12.2 nmol/L)

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

DRUG DATA PROFILES - Psychoactive Agents

Click on a topic below to jump to a specific section. Or use the arrows at the bottom of the page to navigate within this chapter.

TRICYCLIC ANTIDEPRESSANTS

- Amitryptiline

OTHERS

- Clozapine
- Fluoxetine
- Haloperidol
- Lithium

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

AMITRIPTYLINE

CLINICAL USE

- Second-line antidepressant (but particularly dangerous in overdose)
- Blocks serotonin and norepinephrine uptake in the brain
- Active metabolite, nortriptyline, more selective for norepinephrine inhibition
- Nocturnal enuresis in children
- May also be used for neuropathic pain
- May be used for migraine prophylaxis

USUAL DOSE AND DOSE INTERVAL

- Seventy-five milligrams per day initially (less in elderly) at night increasing slowly to 150-200 mg/d
- Nocturnal enuresis: 7-10 y 10-20 mg at night; 11-16 y 25-50 mg at night. Maximum period of treatment 3 months
- Neuropathic pain: 10-25 mg at night up to 75 mg
- Migraine prophylaxis: 10 mg at night up to 75 mg

FACTORS AFFECTING CONCENTRATION

- Metabolism influenced by CYP2D6
- Nortriptyline is an equipotent metabolite
- Self-induction of metabolism
- Enzyme-inducing drugs increase clearance
- CYP3A4 and CYP2C19

TOXIC EFFECTS

- Significant toxicity limits use
- Sedative
- Dangerous in overdose, consequently not recommended in depression
- Tachycardia, arrhythmias and heart block
- Hypomania
- Dyskinesias
- Antimuscarinic effects: dry mouth, constipation, urine retention, increased intraocular pressure

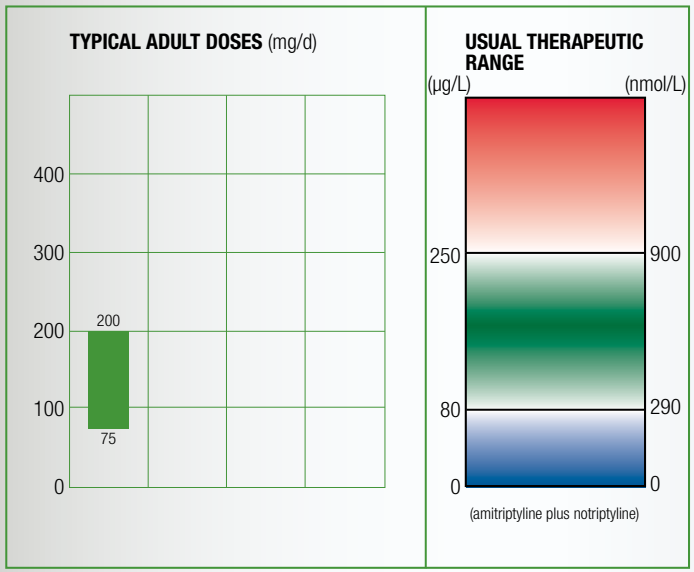
MONITORING THERAPY

- Correlation of plasma concentration and clinical effectiveness is not well documented
- Depression: 50-150 µg/L (180-540 nmol/L)(amitriptyline); better to monitor the sum of amitriptyline and nortriptyline: 80-250 µg/L (290-900 nmol/L)
- Monitoring not required in other conditions

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	2-4 h
Route of elimination	Extensive hepatic metabolism (< 1% excreted renally)
Elimination half-life	17-40 h
Time to steady state	3-8 days of chronic dosing
Protein binding	~95%
Target range	Depression: 80-250 µg/L [sum of amitriptyline and nortriptyline] (290-900 nmol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

CLOZAPINE

CLINICAL USE
- Schizophrenia demonstrated to be intractable to conventional and at least 1 other atypical antipsychotic
- Psychosis in Parkinson's disease

USUAL DOSE AND DOSE INTERVAL
- 12.5 mg on day 1, then 25-50 mg on day 2, increasing in 25-50 mg steps if well tolerated over 2-3 weeks up to 300 mg higher doses to a maximum of 900 mg/d in divided doses can be used

FACTORS AFFECTING CONCENTRATION
- Metabolized by CYP1A2 and CYP3A4
- Norclozapine is pharmacologically active
- The N-oxide metabolite is reduced back to clozapine
- Smoking increases clearance
- Fluvoxamine, possibly other similar SSRIs inhibit clozapine metabolism

TOXIC EFFECTS
- Life-threatening agranulocytosis requires that all patients are enrolled in a patient monitoring service, there are 3 different manufacturers each with their own service. Neutropenia/agranulocytosis occurs in ~3% of patients
- Potentially fatal myocarditis and cardiomyopathy
- Diabetes
- Prostatic hypertrophy
- Dosing must be incremented; administration of a standard dose to a naïve individual could be fatal
- HLA-DRB5*0201 associated with neutropenia

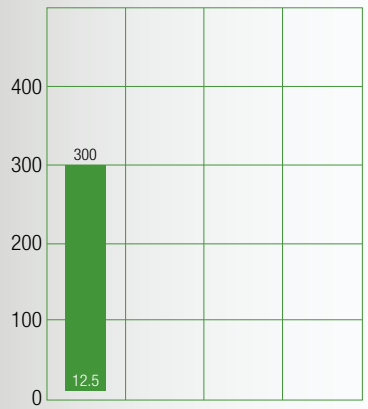
MONITORING THERAPY
- Therapeutic effect may take weeks or months to occur
- MUST monitor differential blood counts due to risk of neutropenia and agranulycytosis
- Optimization of dose through serum concentration monitoring is necessary as full therapeutic effect takes time to develop
- Serum concentrations related to therapeutic and side effects
- Typical ratio of clozapine/norclozapine is 1.32, the ratio can be used as a measure of adherence to therapy

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	~2 h
Route of elimination	Hepatic metabolism (< 1% excreted renally))
Elimination half-life	8-16 h (norclozapine ~ 20 h)
Time to steady state	5-7 days of chronic dosing
Protein binding	~96%
Target range	~350 µg/L (~1100 nmol/L) and clozapine/norclozapine ~1.3

TYPICAL ADULT DOSES (mg/d)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

FLUOXETINE

CLINICAL USE

- First-line antidepressant
- Obsessive-compulsive disorder
- Bulimia nervosa
- Premenstrual dysmorphic disorder

USUAL DOSE AND DOSE INTERVAL

- Depression: 20 mg/d increased after 3-4 weeks as necessary to a maximum of 60 mg/d
- Child: > 8 y, 10 mg after 1-2 weeks increased as necessary to a maximum of 20 mg
- Obsessive-compulsive disorder: 20 mg/d to a maximum of 60 mg/d if required; if no response after 10 weeks reconsider treatment
- Bulimia: 60 mg/d

FACTORS AFFECTING CONCENTRATION

- Prescribed as racemate
- Desmethyl metabolite, norfluoxetine pharmacologically active and has a half-life 4 times that of fluoxetine
- Fluoxetine inhibits CYP2C9, norfluoxetine inhibits CYP3A4, (inhibiting, for example, carbamazepine and phenytoin clearance, respectively)
- CYP2D6 and CYP2C19

TOXIC EFFECTS

- Do not use with monoamine oxidase inhibitors (potentially fatal interaction)
- Care with tricyclic antidepressants
- Hyponatremia
- Gastrointestinal disturbances are common (nausea, dyspepsia, diarrhea)
- Anorexia
- Dyskinesias

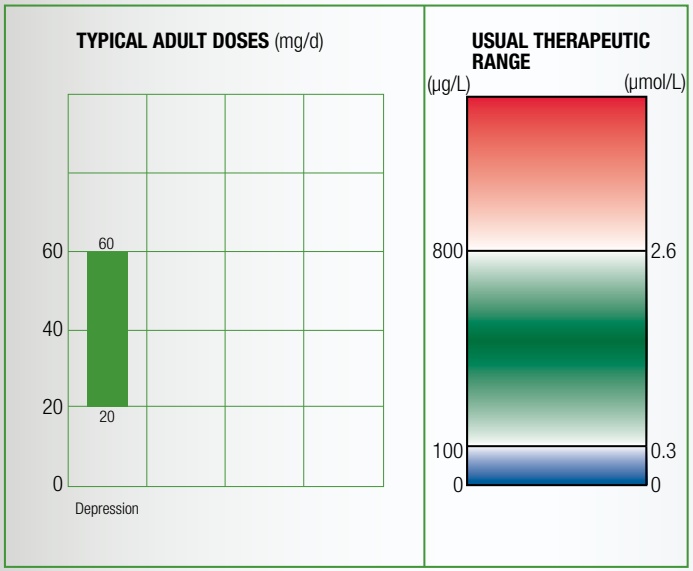
MONITORING THERAPY

- No evidence that monitoring is necessary, but any investigations of concentration-effect relationships should combine fluoxetine and norfluoxetine concentrations

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	6-8 h
Route of elimination	Hepatic metabolism (< 5% excreted renally)
Elimination half-life	Fluoxetine: 24-96 h Norfluoxetine: 170-360 h
Time to steady state	3-4 weeks of chronic dosing
Protein binding	~95%
Target range	Tentatively 100-800 ug/L (0.3-2.6 umol/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

HALOPERIDOL

CLINICAL USE

- Schizophrenia and other psychoses
- Mania
- Violent/dangerous impulsive behavior
- Agitation and restlessness in the elderly
- Anxiety (short-term adjunctive management)
- Intractable hiccup
- Palliative nausea and vomiting

USUAL DOSE AND DOSE INTERVAL

- One-half milligram to 3 mg 2 or 3 times/d or 3-5 mg 2 or 3 times/d in severe or resistant cases, maintain on lowest possible doses, typically 5-10 mg/d; resistant schizophrenia may require 30 mg/d
- Agitation and restlessness: 0.5-1.0 mg once or twice daily
- Anxiety: 0.5 mg twice daily
- Intractable hiccup: 1.5 mg 3 times/d adjusted according to response
- Palliative nausea and vomiting: 1.5 mg once or twice daily, up to 5-10 mg/d if necessary

FACTORS AFFECTING CONCENTRATION

- Metabolized by reduction of the ketone group to an alcohol, this is back-converted to haloperidol by CYP2D6: genotype is important as poor metabolizers will accumulate the reduced metabolite
- Reduced metabolite has 20% of the activity of the parent drug, but has a longer half-life (~70 h)

TOXIC EFFECTS

- Extra-pyramidal side effects
- Irreversible tardive dyskinesia
- Dystonia and akathisia a particular risk in thyrotoxicosis
- Hyponatremia

MONITORING THERAPY

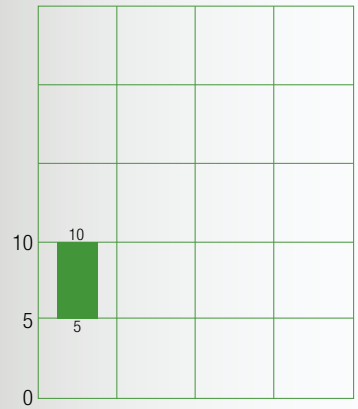
- Monitoring is appropriate in psychoses management, monitoring of the reduced metabolite to avoid cumulation of the reduced metabolite if CYP2D6 genotyping has not been done
- Monitoring in the other conditions is not usually required

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

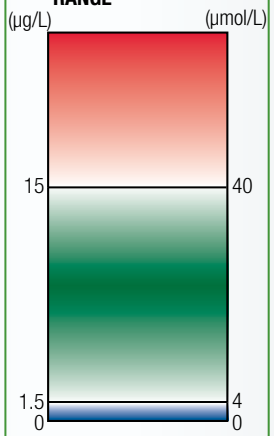
KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	Before a dose (trough sample)
Time to peak	~2 h
Route of elimination	Hepatic metabolism (< 1% excreted renally)
Elimination half-life	~20 h (reduced metabolite accumulates in CYP2D6 poor metabolizers)
Time to steady state	5-7 days of chronic dosing
Protein binding	~90%
Target range	1.5-15 ug/L (4-40 nmol/L) [upper end for management of psychoses – lower end of range may be effective for prophylaxis]; Toxic concentrations vary between patients

TYPICAL ADULT DOSES (mg/d)



USUAL THERAPEUTIC RANGE



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

LITHIUM

CLINICAL USE

- Treatment and prophylaxis of mania and bipolar disorder
- Recurrent depression
- Aggressive or self-mutilating behavior

USUAL DOSE AND DOSE INTERVAL

- Lithium carbonate is the typical salt used: 400-1200 mg/d initially with serum concentration monitoring 12 h post-dose to fall within the target range; adjust as required
- Elderly usually require lower doses
- Once dose stabilized, switch from divided to single doses
- Lithium carbonate 200 mg = lithium citrate 509 mg

FACTORS AFFECTING CONCENTRATION

- Wide bioavailability variation between preparations; changing therapy should be monitored as for initiation of therapy
- Lithium competes with sodium for reabsorption in renal tubules – altered sodium balance or fluid intake may precipitate toxicity
- Interaction with diuretics – thiazides decrease excretion
- Renal impairment

TOXIC EFFECTS

- Renal impairment (risk of vicious circle as drug is renally excreted)
- Hypothyroidism
- Nephrogenic diabetes insipidus
- Hyponatremia potentiates toxicity [avoid thiazide diuretics]
- Hyperparathyroidism rarely
- CNS disturbances (ataxia, tremors, lethargy, sedation, dysarthria, confusion, seizures) are an indication of toxicity
- Chronic dosing:
  – Toxicity > 1.5 mmol/L requires intervention
  – Lithium concentrations > 2.0 mmol/L consider hemodialysis
- Naïve subjects achieving the same concentrations are less likely to suffer significant toxicity

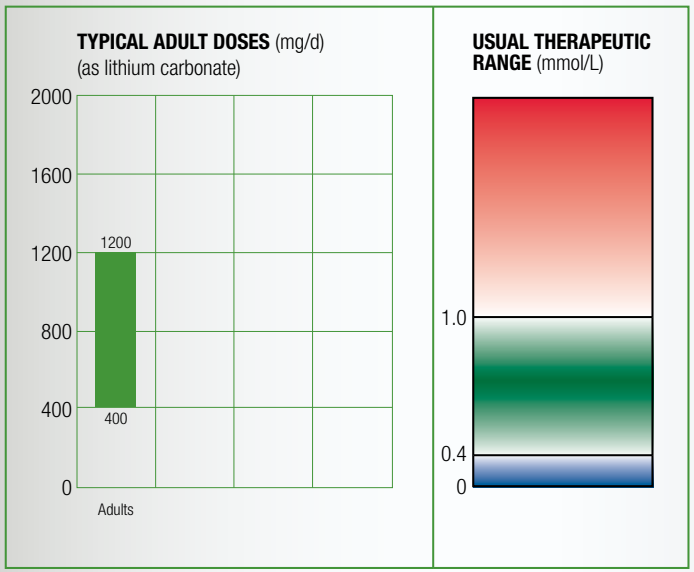
MONITORING THERAPY

- Monitoring is vital
- Check thyroid function and renal function before therapy commences and every 3-6 months
- Target ranges reflect sampling 12 h post-dose
- Target range is 0.4-1.0 mmol/L
- Acute bipolar disorder may require concentrations up to 1.2 mmol/L
- 0.8 mmol/L preferred upper end of target range
- Relapses more likely below ~0.5 mmol/L
- Toxicity is related to concentration

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

KEY PHARMACOKINETIC PARAMETERS

Optimum sampling time	12 h post-dose
Time to peak	2-4 h (longer with sustained-release forms)
Route of elimination	Renal excretion only
Elimination half-life	10-35 h (elderly have decreased renal function and typically longer half-lives)
Time to steady state	3-7 days of chronic dosing
Protein binding	0%
Target range	Usually: 0.4-1.0 mmol/L Elderly: 0.4-0.8 mmol/L Acute bipolar disorder: up to 1.2 mmol/L (Lithium concentration is always expressed as mmol/L or mEq/L)



This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

GLOSSARY

Adherence – the extent to which a patient takes medication as prescribed

Apparent volume of distribution – see *Volume of distribution*

Area under the curve (AUC) – area beneath the plasma concentration-time plot. A measure of the total exposure to drug absorbed

Bioavailability – the fraction of administered dose reaching the systemic circulation unchanged after extravascular administration

Clearance – the ability of the organs of elimination to remove drug from the body. Defined as the theoretical volume of blood which can be completely cleared of drug in unit time

Compliance – see *Adherence*

Concordance – see *Adherence*

Distribution – the movement of drug within the intravascular space and between the intravascular space and extravascular fluids and tissues

Elimination – irreversible loss of drug from the body by metabolism or excretion

Elimination half-life – see *Half-life*

Elimination rate constant – for drugs which follow linear, first-order elimination processes, the fraction of the total amount of drug in the body which is eliminated per unit of time

First-order elimination – elimination process in which the rate of elimination is proportional to the plasma drug concentration

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

GLOSSARY

First-pass metabolism – removal of drug from the plasma after absorption and before reaching the systemic circulation, usually by the liver

Free drug concentration – the concentration of drug in a biological fluid (eg, plasma or serum) that is not bound to protein. The unbound drug is presumed to be the fraction which is pharmacologically active

Half-life – time required for the plasma concentration to fall to half its original value

Loading dose – initial dose to achieve the desired plasma concentration rapidly

Maintenance dose – drug given at intervals to replace drug eliminated from the body and maintain a steady plasma concentration

Nonlinear (zero order) elimination – elimination process in which excretion or metabolism is capacity-limited and may become saturated. Elimination then proceeds at a fixed rate independent of plasma drug concentration. Process is described by Michaelis-Menten kinetics

Peak serum concentration – the maximum serum concentration attained following administration of a dose of drug

Pharmacodynamics – study of the biochemical and physiological effects of drugs and their mechanisms of action. Describes the relationship between the drug concentration at the site of action and the pharmacological response

Pharmacokinetics – study of the absorption, distribution, metabolism and excretion of a drug and its metabolites in the body and of the mathematical relationships which can be used to describe or predict these processes

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

GLOSSARY

Plateau – stable concentration of drug in plasma found at steady state

Steady state – point at which the rate of administration of drug is balanced by the rate of elimination

Target range – the range of plasma concentrations over which a drug exhibits therapeutic benefit with minimal toxicity in the majority of patients

Therapeutic index or **therapeutic ratio** – the margin between the concentration at which a drug exerts a therapeutic effect and the concentration at which toxic effects are observed

Therapeutic range – see *Target range*

Trough serum concentration – the concentration of drug in the serum immediately before the next dose is given, usually representing the lowest concentration achieved on that dose regimen

Volume of distribution –the volume of a compartment necessary to account for the total amount of drug in the body if it were present throughout the compartment at the same concentration as found in the plasma

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

COMMON TRADE NAMES

(not a comprehensive listing for all countries)

TRADE NAME	APPROVED NAME
Advagraf®	Tacrolimus
Amikin®	Amikacin
Cafcit®	Caffeine
Camcolit®	Lithium
Carbagen®	Carbamazepine
Cellcept®	Mycophenolate
Cidomycin®	Gentamicin
Clozaril®	Clozapine
Cordarone®	Amiodarone
Crystodigin®	Digitoxin
Depakene®	Valproate
Depakote®	Valproate
Dilantin®	Phenytoin/Fosphenytoin
Emeside®	Ethosuximide
Epanutin®	Phenytoin/Fosphenytoin
Epilim®	Valproate
Eskalith®	Lithium
Felbatol®	Felbamate
Gabitril®	Tiagabine
Garamycin®	Gentamicin
Gengraf®	Ciclosporin/Cyclosporine
Genticidin®	Gentamicin
Genticin®	Gentamicin
Haldol®	Haloperidol
Keppra®	Levetiracetam
Lamictal®	Lamotrigine
Lanoxin®	Digoxin
Largactil®	Chlorpromazine

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

COMMON TRADE NAMES

TRADE NAME	APPROVED NAME
Lyphocin®	Vancomycin
Lyrica®	Pregabalin
Myfortic®	Mycophenolate
Mysoline®	Phenobarbital/Primidone
Nebcin®	Tobramycin
Neoral®	Ciclosporin/Cyclosporine
Neurontin®	Gabapentin
Norpace®	Disopyramide
Nuelin®	Theophylline
Phyllocontin®	Theophylline
Priadel®	Lithium
Procan®	Procainamide
Procanbid®	Procainamide
Pro-Epanutin®	Phenytoin/Fosphenytoin
Prograf®	Tacrolimus
Pronestyl®	Procainamide
Protopic®	Tacrolimus
Prozac®	Fluoxetine
Rapamune®	Sirolimus
Rhythmodan®	Disopyramide
Sabril®	Vigabatrin
Sandimmun®	Ciclosporin/Cyclosporine
Serenace®	Haloperidol
Slo-Phyllin®	Theophylline
Subutex®	Buprenorphine
Taloxa®	Felbamate

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

COMMON TRADE NAMES

TRADE NAME	APPROVED NAME
Tambocor®	Flecainide
Targocid®	Teicoplanin
Tegretol®	Carbamazepine
Temgesic®	Buprenorphine
Theo-Dur®	Theophylline
Thorazine®	Chlorpromazine
Tobi®	Tobramycin
Tobrex®	Tobramycin
Topamax®	Topiramate
Trileptal®	Oxcarbazepine
Tylenol®	Acetaminophen
Uniphyllin®	Theophylline
Vancocin®	Vancomycin
Vimpat®	Lacosamide
Xylocaine®	Lidocaine
Zarontin®	Ethosuximide
Zonegran®	Zonisamide

THERAPEUTIC DRUG MONITORING

INTERACTIVE CLINICAL GUIDE

Table of Contents

This is an Interactive PDF. To navigate, please click on the chapters in the table of contents above. Then use the arrows at the bottom right corner of the page to navigate within each chapter. For more information, please visit www.abbottdiagnostics.com.

Click here to return to page 1.

For more information, please visit www.abbottdiagnostics.com.

Put science on your side.

Abbott
A Promise for Life