Therapeutic Drug Monitoring (TDM)

An Educational Guide

Answers for Life.

SIEMENS
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Therapeutic Drug Monitoring (TDM)—An Overview

Siemens Healthcare Diagnostics continues to deliver on its commitment to complete the development of a comprehensive therapeutic drug monitoring (TDM) menu on the ADVIA Centaur® systems, ADVIA® Chemistry systems, IMMULITE® systems, Dimension® RxL Max and Xpand Plus, Dimension Vista® system, V-Twin®, and Viva-E® drug testing systems. The goal of menu expansion has been to provide a menu broad enough to satisfy any laboratory’s TDM testing needs. Combined with productive and adaptable instrumentation, Siemens delivers the throughput and flexibility that customers demand.

The purpose of this TDM educational guide is to:
- Provide an overview of the history of Therapeutic Drug Monitoring
- Define the role of TDM testing in patient care
- Highlight factors that affect results and interpretation
- Describe the drugs that are most frequently monitored and the methods used to monitor them

History

The science of Therapeutic Drug Monitoring grew out of the recognition that:
- Certain drugs have a narrow therapeutic range
- In concentrations above the upper limit of the range, the drug can be toxic
- In concentrations below the lower limit of the range, the drug can be ineffective
- Not all patients have the same response at similar doses

These findings led to the development of Clinical Pharmacology departments, whose job it was both to provide the testing and to perform the studies needed to determine the therapeutic ranges and factors that affect results generation and interpretation.

However, not everyone embraced TDM testing. Some believed that TDM testing provided little or no value, and that a clinician could achieve the same results by prescribing the drug based on an understanding of the drug’s biochemistry and the patient’s clinical profile, then adjusting the dose based on the patient’s clinical response.¹

There was truth to be found in both arguments.

Studies were initiated to determine the clinical value of TDM testing, and in certain instances clear clinical value was demonstrated. Today there are over 20 therapeutic drugs which are routinely monitored.

Current TDM Testing Indications

The studies mentioned above helped establish the criteria used to determine if a particular drug therapy could be monitored simply via clinical response, or if TDM testing is needed (see table below.) Toxicty can manifest clinically in a way that is very similar to the underlying disease. In these cases, the value of TDM is discovering drug toxicity before irreparable harm is done.

In order for some drugs to be effective and non-toxic, TDM testing is required to ensure the patient maintains a concentration of drug within his system that is within the established therapeutic range. This remains the essential underlying value of TDM testing for both the clinician and the patient.

<table>
<thead>
<tr>
<th>Indications for TDM Testing², ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug efficacy difficult to establish clinically (Phenytoin)</td>
</tr>
<tr>
<td>Suspected toxicity</td>
</tr>
<tr>
<td>Inadequate therapeutic response</td>
</tr>
<tr>
<td>Compliance concerns</td>
</tr>
<tr>
<td>Dosage change</td>
</tr>
<tr>
<td>Change in patient’s clinical state</td>
</tr>
<tr>
<td>Change in co-medications (Quinidine decreases digoxin clearance)</td>
</tr>
<tr>
<td>Manifestations of toxicity and disease state are similar (Theophylline)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TDM Testing not Indicated², ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity is not a realistic concern (Penicillin)</td>
</tr>
<tr>
<td>Effects can be measured using functional laboratory tests (Anticoagulants)</td>
</tr>
<tr>
<td>Plasma concentration not predictably related to effects (Anticoagulants)</td>
</tr>
<tr>
<td>Effect of the relationship remains undefined (Antidepressants)</td>
</tr>
</tbody>
</table>
Interpretive Criteria

Introduction
Measuring the blood concentration of certain therapeutic drugs is only one aspect of effective TDM monitoring. Because therapeutic ranges are not absolutes, in many instances expert clinical interpretation of the value is necessary to derive meaning from the result. True TDM testing takes into consideration all the factors that can affect results, as well as all the factors that can affect interpretation, as described below.

Applicability of Therapeutic Ranges
Therapeutic ranges are recommendations derived by observing the clinical reactions of a small group of patients taking the drug. The lower limit (trough) is set to provide ~50% of the maximum therapeutic effect, while the upper limit (peak) is defined by toxicity, not therapeutic effect. It is not unusual for some patients to achieve therapeutic effects at levels below the established range. Others may experience toxicity while still in the established range.1,2

Factors that Affect Results
Many factors contribute to the production of an accurate and meaningful drug level measurement:

- Pharmacokinetics
- Pharmacodynamics
- Dose
- Sampling time and type
- Testing methodology
- Genetic polymorphisms

Major Sources of Pharmacokinetic Variability1
- Patient Compliance – lack of
- Age – neonates, children, elderly
- Physiology – gender, pregnancy
- Disease – hepatic, renal, cardiovascular, respiratory
- Drug-to-drug interactions
- Environmental influences

Pharmacokinetic variability describes the relationship between the dose administered and the resulting plasma concentration. This relationship can be affected by differences in the way a patient's system absorbs, distributes, metabolizes, and/or eliminates the drug – in other words one dose does not fit all. Some major sources of pharmacokinetic variability are listed in the table above. Pharmacokinetic variability can be greatly reduced by adjusting doses to maintain plasma drug concentrations within a therapeutic range.4

Pharmacodynamic variability describes the way in which the drug affects the body's functions, and the relationship between the drug's chemical structure, actions, and effects.5

Sampling time is also critical, since the drug concentration varies over the entire dosing interval and with the duration of dosing in relation to achieving a steady state. Trough values, those obtained just prior to dosing, are the least variable concentrations and are most often used to establish therapeutic ranges. Drugs with short half-lives, in relation to the dosing interval, require trough concentration monitoring. Drugs with a long half-life can be monitored at any point in the dosage interval.

Additional consideration should be given to the type of sample tested as some anticoagulants may interfere with results for certain drugs (lithium heparin affects lithium results), while some gel separators interfere with the results of other drugs.2 Likewise, the sensitivity and specificity of the testing methodology must also be considered.2

Factors that Affect Interpretation
The factors that affect result interpretation vary from drug to drug. For example, a digoxin concentration must be interpreted in light of the creatinine and potassium concentrations, the presence of acidosis or the administration of interacting drugs as well as the patient's clinical state.2 When determining the appropriate lithium dose or interpreting lithium results, knowing if a woman is pregnant is key, as dose requirements increase due to increased renal clearance.4

The table on the following page lists the sample information required for accurate interpretation of a drug concentration. The interpreting clinician should also have a good understanding of the drug and its action, particularly how protein binding and active metabolites can affect results.

Protein Binding
TDM assays typically require serum or plasma and usually measure both the bound and unbound drug, even though it is the unbound drug that reacts with the receptor to produce a response. This is seldom an issue – unless the patient's binding capacity is altered due to disease-state, drug interaction, or non-linear binding. In such cases, the effect of the protein binding needs to be taken into consideration when interpreting results.5
Commonly Monitored Drugs

Introduction
There are several classes of drugs commonly monitored to ensure correct blood concentration, including the following:

- Antiepileptics
- Antiarrythmics
- Antibiotics
- Antineoplastics
- Antimanics
- Bronchodilators
- Immunosuppressives

The goal of this chapter is to briefly overview each of these classes and some of the more common drugs within each class, particularly those run on the ADVIA Centaur, ADVIA chemistry, IMMULITE immunoassay, Dimension Vista, Dimension Integrated chemistry, Viva-E, and V-Twin drug testing systems. A table that summarizes this section is located in the Appendix.

Antiepileptics
Overview
This class of drugs, also known as anticonvulsants, is most often prescribed for the management of epilepsy, though it may also be prescribed for other indications such as tic douloureux, myotonia, bipolar effective disorder, prophylaxis of certain varieties of migraine and of cardiac dysrhythmia. All antiepileptic drugs are capable of depressing abnormal neuronal discharges in the central nervous system, which may otherwise result in seizures. Other drugs in this category, such as clonazepam and sulthiame, do not require monitoring.

Sample Information Required for Accurate Interpretation

- Time of sample in relation to last dose
- Duration of treatment with the current dose
- Dosing schedule
- Age, gender
- Other drug therapy
- Relevant disease states
- Reason for request (e.g. lack of effect, routine monitoring, suspected toxicity)

Active Metabolites
Many therapeutic drug metabolites, though not measured, contribute to a drug’s therapeutic response. For example, primidone treatment is monitored by measuring phenobarbitone, an active metabolite, but primidone itself and other metabolites are also active.

Other Considerations

Steady State
Steady state is defined as the point at which drug intake and elimination reach an equilibrium, and the height of the peak and the depth of the trough are predictable. Steady state is reached after 5-6 half lives of the drug. The goal of therapeutic drug monitoring is to optimize the drug dose so the patient's drug concentrations remain within the therapeutic range for the drug.

Unless a so-called loading dose (high initial dose) or i.v. infusion is used initially, steady state must be reached before meaningful TDM is possible for those drugs that are given long-term.

Turnaround Time
Turnaround time is also important to ensure that the physician has time to evaluate the result before the patient is scheduled to receive his next dose. For most therapeutic drugs this is not an issue, as assays for the most commonly tested analytes are available on several fully automated analyzers. However, for drugs without commercially available assays, highly specialized chromatographic and ultra-filtration assays are used. These methods require specially trained staff and are most often performed in a limited number of sites. Therefore, results tend to take longer to receive.

Summary
The goal of TDM testing extends beyond simply measuring the amount of a particular drug in the patient’s system. It also involves the interpretation of those results in light of other clinical and biochemical considerations to evaluate the effectiveness of therapy and improve patient outcomes. Only after considering all contributing factors can a physician assess, and if necessary modify, a particular course of therapy.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (TEGRETOL)</td>
<td>Used to treat psychomotor seizures, tonic-clonic seizures, and mixed seizures. Often given with phenytoin. Also used to treat trigeminal and glossopharyngeal neuralgia pain</td>
<td>4 – 10 µg/mL</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Effective means of preventing absence (petit mal) seizures</td>
<td>10 – 150 µg/mL</td>
</tr>
<tr>
<td>Primidone</td>
<td>Monitoring serum Primidone concentration is the most effective means of improving seizure control and reducing the risk of toxicity</td>
<td>2.5 – 20 µg/mL</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Effective therapy for febrile seizures and neonatal seizures</td>
<td>15 – 40 µg/mL</td>
</tr>
<tr>
<td>Phenytoin (DILANTIN)</td>
<td>Corrects tonic-clonic seizures. Often used instead of phenobarbital</td>
<td>10 – 20 µg/mL</td>
</tr>
<tr>
<td>Valproic Acid (DEPAKENE)</td>
<td>Used to treat petit mal, tonic-clonic, and myoclonic seizures. Monitoring this drug is important because its pharmacokinetics are unpredictable</td>
<td>50 – 100 µg/mL</td>
</tr>
</tbody>
</table>

**Test Methods**
These drugs are most commonly tested with serum or plasma using any of the several commercially available immunoassays. While convenient and cost-effective, some of the antibodies used in these assays can cross-react with the metabolite in question. A more sensitive and specific alternative is HPLC. However due to high cost and long time to result, it is not used routinely.

**Antiepileptic Drug Monitoring Indications**
- Soon after steady-state conditions are initially expected
- When the patient is seizure-free and experiencing no adverse effects (determines therapeutic concentration)
- When questioning an over-dose
- To determine the cause of relapse
- Before and after any change in dose
- Before and after introducing a drug that may interact

Whole plasma drug concentrations are most often measured. Unbound plasma concentrations may be requested when a physician suspects that the patient’s protein binding capacity for the drug may be altered due to pregnancy, disease, malnutrition, or drug interaction.

**Test Timing**
Trough concentrations are most often obtained for monitoring purposes because they provide the most consistent concentration values from dose to dose. Peak concentration testing is not recommended.

**Therapeutic Ranges**
Therapeutic ranges for antiepileptic drugs should be used to help determine the optimal therapeutic concentration for an individual patient, as one patient’s optimal therapeutic concentration may fall into the toxic range, while another’s may fall below the established therapeutic range.

**Application of Therapeutic Ranges for Antiepileptic Therapies**
- Guide treatment before the clinical response has had time to become clear
- Determine cause of treatment failure
- Aid in the diagnosis of symptoms that may represent drug over-dosage

**Antiarrhythmics**
**Overview**
Arrhythmia is a disorder that may result in cardiac abnormalities. They are classified as either tachycardia (fast heartbeat, > 100 bpm) or bradycardia (slow heart beat, <60 bpm). Antiarrhythmic agents are used to control the rate and rhythm of the heart beat. This class of drugs is segregated into four sub classes based on the action of the drug. Many of the drugs in class I require frequent monitoring, and are therefore being displaced by the class II and III drugs, which require less monitoring.
### Antiarrhythmic Drug Classes

- **Class I** – Block the fast sodium current
- **Class II** – Block the effects of catecholamines
- **Class III** – Prolong action potential and hence refractoriness by blocking K+
- **Class IV** – Block the cardiac calcium

**NOTE:** Digoxin and digitoxin do not fall neatly into any of these categories, though they are undoubtedly cardiac agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitoxin</td>
<td>Used to improve cardiac contraction in congestive heart failure and to correct supraventricular tachycardia</td>
<td>10 – 30 ng/mL</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Used to improve cardiac contraction in congestive heart failure and to correct supraventricular tachycardia</td>
<td>0.9 – 2 ng/mL</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Antiarrhythmic</td>
<td>1 – 30 µg/mL</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Monitoring lidocaine in serum during infusions helps to establish and maintain adequate prophylactic or therapeutic drug concentrations and avoid toxicity</td>
<td>1.5 – 5 µg/mL</td>
</tr>
<tr>
<td>NAPA</td>
<td>Measurement of N-acetylprocainamide, together with procainamide concentrations help to achieve an optimum antiarrhythmic effect and reduce the risk of toxicity</td>
<td>10 – 30 µg/mL</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Monitoring serum procainamide concentrations helps to achieve an optimum antiarrhythmic effect and reduce the risk of toxicity</td>
<td>4 – 12 µg/mL</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Monitoring serum quinidine concentrations, along with clinical assessment, is the most effective means of achieving an optimum antiarrhythmic effect and reducing the risk of toxicity</td>
<td>0.5 – 8 µg/mL</td>
</tr>
</tbody>
</table>

### Test Methods

Antiarrhythmic drugs are most commonly tested with plasma using any of the several commercially available immunoassays. Digoxin is the most commonly monitored therapeutic drug. Most competitive assays are precise and accurate but some cross-react with digoxin-like immunoreactive factor (DLIF) and common steroids. ADVIA Centaur and EMIT® assays from Siemens are proven not to cross-react with DLIF or many common steroids. Data establishing this is provided in the package insert.

### Test Timing

For all antiarrhythmic drugs, samples should be collected at least 6 hours (preferably 8) post dose to allow for absorption and distribution.

### Therapeutic Ranges

For patients with normal renal function, who have achieved steady-state levels, the therapeutic range for digoxin is based on blood samples obtained 8 hours after the last dose. Testing of earlier samples may produce falsely elevated results. Numerous factors affect the action of these drugs. Agents with significant interactions with digoxin include cholestyramine, heparin, phenobarbital, phenytoin, rifampin, and possibly quinidine. The agent with the most pronounced and potentially dangerous interaction to digoxin is quinidine.

### Antibiotics

**Overview**

Most of the drugs in this class have wide therapeutic ranges and therefore do not require therapeutic monitoring. However, those with narrow therapeutic ranges require monitoring to avoid potentially irreversible toxicity. Still others are monitored on a case-by-case basis. Gentamicin and Tobramycin are aminoglycoside antibiotics most commonly used for infections by resistant gram-negative organisms. Vancomycin is glycopeptide antibiotic used to treat life-threatening infections caused by gram-positive cocci. Due to the emergence of vancomycin-resistant organisms, it has been recommended that its use be restricted to treating methicillin-resistant Staph aureus and ampicillin-resistant enterococcal infections.
Drug Indication Therapeutic Range

**Amikacin**
Used to treat different types of bacterial infections. Most often used to treat severe infections with multidrug resistant gram-negative bacteria
Peak: 15 – 30 µg/mL
Trough: 1 – 10 µg/mL

**Gentamicin**
Given to patients with potentially life-threatening bacterial infections. Excess dosage can cause kidney and auditory nerve damage
Peak: 5 – 10 µg/mL
Trough: 1 – 2 µg/mL

**Netilmicin**
Used to treat serious infections, particularly those resistant to gentamicin
Peak: 1 – 12 µg/mL

**Tobramycin**
Gentamicin and tobramycin have identical antibacterial spectra, though tobramycin is more active against Pseudomonas aeruginosa
Peak: 5 – 10 µg/mL
Trough: 0.5 – 2 µg/mL

**Vancomycin**
Inhibits synthesis of the bacterial cell wall. Most commonly prescribed for serious, life-threatening infections by gram-positive cocci
Peak: 30 – 40 mg/mL
Trough: 5 – 10 mg/mL

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**Test Methods**
These drugs are most commonly measured by immunoassay. HPLC can also be used for many of these drugs, with the exception of Gentamicin, which is not a single substance. In the past, clinicians have made an issue of immunoassay sensitivity, however today’s assays are widely accepted as meeting clinical needs.

**Test Timing**
Unlike most other TDM regimens that strive to achieve a consistent therapeutic level of the drug in the patient’s bloodstream, aminoglycoside therapy strives to achieve a high peak, followed by a low trough to avoid accumulation. Under traditional dosing regimens, this requires monitoring of both peak (~0.5 hours after transfusion) and trough (within 0.5 hours of the next dose) concentrations, which may be frequently repeated until results stabilize.

For Vancomycin, peak levels do not correlate with either efficacy or toxicity. However, trough values are monitored to ensure that the drug level remains above the minimum inhibitory concentration (MIC) for the organism. The dose and the condition of the patient should determine the frequency of testing.

Antibiotic drug monitoring is not always necessary. During once-daily dosing, toxicity is less of an issue, and monitoring less necessary, though peak values could remain useful in optimizing the individual’s dose. It has been suggested that aminoglycoside and vancomycin therapy for uncomplicated infections in patients with normal renal function does not require monitoring.

**Therapeutic Range**
There are established ranges for trough and peak concentrations during traditional aminoglycoside therapy. However, there are no established ranges for once-daily dosing, as the accumulation is not an issue and the efficacy of the dose is well established.

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**Antimanics**
Overview

<table>
<thead>
<tr>
<th>Antimanics Drugs</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Used to treat bipolar disorders and to supplement other antidepressant drugs</td>
<td>Peak: 0.6 – 1.2 mmol/L</td>
</tr>
</tbody>
</table>

Test Methods
Immonoassay is the most common method used for monitoring these drugs.

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**Antineoplastics**
Overview

<table>
<thead>
<tr>
<th>Antineoplastic Drugs</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Used in the treatment of neoplastic disorders</td>
<td>Peak: 0.1 – 2600 µmol/L</td>
</tr>
</tbody>
</table>

Test Methods
Immonoassay is the most common method used for monitoring these drugs.

*recommended concentrations can vary depending on the infection severity*
Bronchodilators

Overview
Theophylline is one of the most commonly used bronchodilators. It is primarily used to treat patients with chronic asthma. Monitoring is necessary due to the drug’s highly variable inter-individual pharmacokinetics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>For use in the quantitative analysis of caffeine levels in human serum in subjects undergoing therapy with caffeine, especially in cases of neonatal apnea</td>
<td>Peak: 1 – 30 µg/mL</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Used to relax smooth muscles in bronchi and pulmonary blood vessels</td>
<td>10 – 20 µg/mL</td>
</tr>
</tbody>
</table>

Test Methods
Immunoassay is the most common method used for monitoring these drugs.

Test Timing
Trough levels are usually measured after the patient has achieved a steady state.

Therapeutic Range
Several factors must be considered when interpreting the results:
- Patient’s liver function
- Co-administered drugs
- Smoker/non-smoker
- Preparation used (pill or injectable)
- Neonate or adult

Immunosuppressants
TDM testing is a critical aspect of immunosuppressive drug therapy. Optimizing drug dosing is not only key to avoiding rejection, but also in reducing the severe side effects of these drugs (infections, cancer, weight gain, hypertension, and possible liver or kidney failure), which often prompt patient non-compliance. The strategy is to employ a combination of drugs in doses that prevent acute rejection and loss of graft function without compromising overall health. Transplant patients are prescribed immunosuppressive drugs as lifelong maintenance therapy and most drugs are routinely monitored.

Drug Indication Therapeutic Range

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (NEORAL, SANDIMMUNE)</td>
<td>Aids in the management of cyclosporine therapy in kidney, heart, and liver transplant patients</td>
<td>50 – 350 µg/L</td>
</tr>
<tr>
<td>Everolimus (CERTICAN)</td>
<td>Aids in the management of certican therapy in kidney and heart transplant patients</td>
<td>3 – 8 µg/mL</td>
</tr>
<tr>
<td>Mycophenolic Acid (CELLCEPT, MYFORTIC)</td>
<td>Aids in the management of mycophenolate mofetil therapy in transplant patients</td>
<td>1 – 4 µg/mL</td>
</tr>
<tr>
<td>Tacrolimus (PROGRAF)</td>
<td>Aids in the management of tacrolimus therapy in kidney, heart, and liver transplant patients</td>
<td>3 – 15 µg/L</td>
</tr>
<tr>
<td>Sirolimus (RAPAMUNE)</td>
<td>Aids in the management of rapamune therapy in kidney transplant patients.</td>
<td>3 – 15 µg/mL</td>
</tr>
</tbody>
</table>

Test Methods
Immunoassay is the most common method used for monitoring these drugs.

Test Timing
Immunosuppressive drug testing typically decreases over time after transplant.

Therapeutic Range
The therapeutic ranges of immunosuppressive drugs refer to trough levels. Ranges may vary with indication and if immunosuppressive therapy is given concurrently.

Summary
TDM testing is performed to ensure that drug concentration is within the established therapeutic range in order for the drug to be effective and to not cause drug toxicity. Therapeutic ranges are absolutes, so in most instances expert clinical interpretation of the values is not necessary to derive meaning from the result. The common classes of drugs used to monitor to ensure correct blood concentration include antiepileptics, antiarrythmics, antibiotics, antineoplastics, bronchodilators, and immunosuppressives. The majority of new advances and developments for Therapeutic Drug Monitoring are in immunosuppressive and anti-retroviral drugs.
Pharmacokinetics

Overview
Pharmacokinetics is the study of what the body does to a drug after administration. It is divided into four categories: Absorption, Distribution, Metabolism and Excretion.

Major Pharmacokinetics Processes Affecting Drug Concentration

Absorption
Absorption refers to the ability and process of a dosage reaching the bloodstream. There are different routes of drug administration. The most common are:

- Oral
- Intramuscular
- Subcutaneous
- Rectal
- Transdermal
- Intravenous

Drugs administered intravenously do not require absorption since they immediately reach the vascular system. Oral agents must first be absorbed into the GI tract and may be metabolized there or by hepatic enzymes prior to reaching the circulation. Transdermally administered drugs do not pass through either the GI tract or the liver. The rate of absorption and extent of absorption are dependent on various factors such as:

- Drug formulation
- Manufacturer
- Route of administration
- Intra-individual variations

Another aspect of absorption is bioavailability. This is the fraction of the administered dose that reaches the systemic circulation. Bioavailability is 100% for IV injection.

Distribution
Once the drug is absorbed, a certain drug concentration is reached in the body. The volume in which the drug is distributed is a product of the drug's dose divided by the plasma concentration.

\[ V_d = \frac{\text{dose}}{\text{plasma concentration}} \]

The distribution phase represents the early period in the dose/time curve when the drug is being circulated in the blood throughout the body and into the body fluids, organs and tissues. Vd is directly related to the half-life of the drug. A drug with a large Vd compared to a drug with a small Vd, given similar clearance rates, will have a longer half-life and remain in the body longer.

Half-life refers to the time required for the concentration of the drug in the body to be reduced by one half. For example, if a drug has a half-life of four hours, four hours after the initial dose, 50% of the drug will be removed. Eight hours after the initial dose, half of the remaining drug (25% of total) will be removed, for a total of 75% having been removed at that time, and so on. Half-life information is used to determine the correct drug dose required to attain the desired therapeutic range.

Metabolism
Drug metabolism occurs primarily in the liver, and also in the GI tract. Drug metabolism is the process in which the body breaks down and converts the drug into active chemical substances. Knowing how the drug is metabolized is important for several reasons. When two or more drugs are administered at similar times how they metabolize will impact any drug interactions. In addition, drug metabolites can be either protein bound (inactive) or free (active). The drug dosage will depend on how the drug metabolizes. Factors that impact drug metabolism include genetics, environment, nutrition, and age.

Excretion
Drug excretion from the body occurs through the kidneys, or fluids excreted through the lungs, GI or skin. Renal dysfunction reduces drug clearance and may contribute to drug accumulation and increased risk of adverse drug effects.
Use of Pharmacokinetic Studies
Clinical pharmacokinetic studies are performed to examine the absorption, distribution, metabolism and excretion of a drug under investigation in healthy volunteers and/or patients. The study outcomes are useful for determining the appropriate use of medicines according to patient characteristics, such as disease and for predicting the influence of drug interactions. The results can also provide information for TDM.

Therapeutic Drug Monitoring and pharmacokinetic studies help the physician provide optimum care by:

- Helping the physician initiate therapy to achieve the maximum therapeutic effect for the patient in the shortest amount of time
- Minimizing the risk of drug toxicity
- Ensuring drug side effects are controlled and minimized

Pharmacokinetic studies can also help determine and evaluate the loading dose. The loading dose is a relatively large amount of drug which is administered over a short period of time to quickly move the patient’s serum drug concentration toward a level that will achieve desired patient response.

After a loading dose, another dosing regime is needed to maintain the patient's serum drug concentration. The maintenance dose is the amount of the drug and the dose frequency needed to achieve a steady state at the desired therapeutic concentration.

Therapy is achieved when the desired effect is attained because the required concentration has been reached. That concentration would set the lower limit of utility of the drug, called the Minimum Effective Concentration (MEC). Some drugs exhibit side effects and at higher concentrations may be toxic. At some concentrations, these toxic effects become dangerous. That concentration is called the Maximum Therapeutic Concentration or Minimum Toxic Concentration (MTC). Patient studies have generated upper (MTC) and lower (MEC) plasma concentration ranges that are deemed safe and effective in treating disease. These concentrations are known as the “therapeutic range” for the drug.

In a dosing study it is important to take into consideration the peaks and troughs of drug levels following dose administration (see graph below). Blood samples are drawn at a prescribed time after the dose is administered to capture the peak level, or the high point of serum drug concentration. Another sample must be drawn prior to the next dose to capture the trough level, or the lowest point of the serum drug concentration. The timing depends on the type of drug, route of administration and absorption. Accurately timing the drug administration and sample collection is critical. This will ensure that the sample represents the true peak and trough concentrations which will ensure that the patient’s dosage will be adjusted accurately.

Summary
TDM testing is used in patient care to ensure the patient achieves the maximum therapeutic effect in the shortest amount of time, minimize the risk of drug toxicity and identify which drug is appropriate for diagnosis. The four categories of pharmacokinetics include distribution, absorption, excretion and metabolism. Drug administration is commonly administered orally, intramuscularly (IM), subcutaneously, rectally, transdermally, and intravenously (IV). It is important to draw the blood right before the dose is administered and then right again before the next dose is administered.
TDM Technologies

Over the past three decades the advancements in TDM monitoring methods have led to more sensitive and precise assays, with faster turnaround times, resulting in better patient drug management. Traditionally chromatographic methods were employed, which had good specificity and sensitivity but were too labor intensive. The advent of immunochemical assays, along with automation, meant faster, less labor intensive and more reliable TDM results. They became the market drivers for TDM testing.

HPLC: High Pressure Liquid Chromatography is a common analytical method used to measure therapeutic drug levels prior to the advent of immunoassays. The principle of HPLC technology is based on the fact that separation of a substance depends on the relative distribution of mixture constituents between two phases, a mobile phase (carrying the mixture) and a stationary phase. Substances that are distributed preferentially in the mobile phase move through the system more rapidly than do the substances that are distributed in the stationary phase.

The basic pathway in HPLC involves six elements:
1) Solvent (mobile phase) reservoir
2) Pump
3) Sample injector
4) Column
5) Detector
6) Output data-processing unit

In HPLC, a liquid containing the sample is injected at one end of the column. The column contains a medium which helps separate the molecules in the liquid. High pressure is used to overcome the resistance to flow. As the liquid flows, some molecules move faster than others due to differences in solubility and polarity. The exact time that each molecule takes to flow through the column is measured by a detector. The retention time is calculated. An internal standard, a compound similar in structure to the specimen to be analyzed, is also run through the column. By comparing the retention time of the sample to the internal standard, the molecule (or drug) can be identified. The concentration of the molecule can also be determined from the peaks produced during the run. The peak size is used to calculate the quantity of the drug in the specimen.

GC/MS: Gas-liquid chromatography is a separation method using very high temperatures to cause sample vaporization. Vaporization separates the various molecules in the samples into their different fractions. The time required for the molecules to traverse the system and the number of molecules that reach the endpoint identify the drug. In mass spectrophotometry the vaporized fractions are passed through an electrical field. The molecules can be separated on the basis of molecular weight. The pattern of separation is unique to each drug and therefore establishes a “fingerprint” for identification. GC/MS is the gold standard method for the identification of drugs of abuse. Its great sensitivity and reliability along with good specificity and accuracy are the strengths of this method.

However, its weaknesses have led labs to find other methods. The weaknesses include:
- Labor-intensive
- Specially trained operators required
- Expensive
- Turnaround time can be slow

LC/MS (Liquid Chromatography Mass Spectrometry):
All chromatography-based techniques work on the principle that different substances are absorbed differently in solution. Two “phases” or materials are used to separate the components of a solution. The mobile phase carries the sample along the stationary or solid phase, which separates out the components in the sample. In LC, an organic solvent moves an extract of sample through a resin column. The sample components are detected as they exit the column. LC/MS combines LC with mass spectrometry, which identifies substances by their molecular weight. The individual sample components are separated and shattered into representative fragments. These are recognized by: retention time, molecular weight and fragmentation spectrum.

Because the molecular weight and fragmentation spectrum for each substance is unique, this method is comparable to fingerprinting in terms of specificity. Tandem mass spectrometry (tandem mass spec, MS/MS) involves multiple steps of mass spectrometry with the fragmentation occurring between steps.
RIA: Not commonly used any longer due to waste disposal issues, RIA or Radioimmunometric assays, use radioactivity to detect the presence of the analyte. In RIA, the sample is incubated with an antibody and a radio-labeled drug. The amount of radioactivity measured is compared to the radioactivity present in known standards which are included in each run. Results are quantitative.

In RIA the specimen is mixed with a specific antibody to the drug being analyzed as well as a known quantity of the same drug labeled with radioactive iodine. The drug in the sample and the radioactive labeled drug compete for sites on the antibody. The sample is washed to remove unbound radioactive drug. A gamma counter is then used to measure the amount of radioactivity in the sample as counts per minute (CPM). This number is inversely proportional to the amount of drug in the sample.

The strengths of the RIA method are sensitivity and reliability. Low cost is achievable in high volumes. Weaknesses of this method include the special handling and disposal costs of radioactive material. QC and standards must be performed with each run, leading to extra labor and cost.

PETINIA: An immunoturbidimetric method that is used today for TDM testing is PETINIA or Particle Enhanced Turbidimetric Inhibition Immunoassay. This method uses the creation of light scattering particles to measure drug levels. The latex particle-bound drug binds to the drug-specific antibody, forming insoluble light-scattering aggregates. This causes an increase in the turbidity of the reaction mixture. Non-particle-bound drug in the patient sample competes with the particle-bound drug for antibody binding sites, inhibiting the formation of insoluble aggregates. The rate of particle aggregation (turbidity) is inversely proportional to the concentration of drug in the sample. Therefore the rate of increase of absorbance (hence the rate of the increase in turbidity,) is inversely proportional to the concentration of the drug.

EIA: EIA or enzyme immunoassay became the next generation of immunoassays after RIA. EIA uses a non-radioactive enzyme label. This eliminates the need for special handling and reduces disposal costs. Most of the drug testing today is performed using homogeneous EIA techniques. This refers to the fact that the assays are performed in a single step, i.e. only one antibody is used in the procedure. Therefore, the turnaround time for testing is reduced.

EMIT: The EMIT (Enzyme Multiplied Immunoassay Technique) homogeneous enzyme immunoassay is a versatile methodology designed to measure microamounts of drugs and drug metabolites in human biological fluids. The EMIT technology is based on competition for the target analyte antibody binding sites. Analyte in the sample competes with the drug in the enzyme reagent that is labeled with G6PDH. Active enzyme G6PBH converts the coenzyme (NAD) in the antibody reagent to NADH, resulting in a kinetic absorbance change that is measured photometrically.

FPIA: Fluorescence Polarization Immunoassay. This method uses a fluorescent molecule as the label instead of an enzyme, making it more sensitive. In FPIA, the patient sample is incubated with a known quantity of the fluorescent-labeled drug and an antibody specific for the drug. As in EMIT, the labeled and unlabeled drugs compete for the binding sites of the antibody. Polarized light is emitted in certain angles depending on whether the fluorescent-labeled drug is bound to antibodies or not. Since this is a competitive assay, the greater the amount of drug in the sample, the lower the amount of fluorescence.

Chemiluminescence: This is a chemical reaction that emits energy in the form of light. When used in combination with immunoassay technology, the light produced by the reaction indicates the amount of analyte in a sample. The most common chemiluminescent assay methods are either enzyme-amplified or direct chemiluminescent measurements.

A competitive assay is used in measuring TDMs with the chemiluminescent method. In direct chemiluminescence, such as the ADVIA Centaur system, the acridinium ester (AE) is used as the label and is directly conjugated to the drug. The sample is incubated with the AE-labeled drug, and the drug specific antibody. Once the AE is oxidized by hydrogen peroxide and the sample becomes alkaline, a light emission occurs. The lower the drug concentration in the sample, the greater the light emission. This is due to the small AE molecule, which decreases the blockage of binding sites and increases diffusion rates.

An example of an enzyme-amplified chemiluminescence method is the IMMULITE system. The endpoint is a sustained light signal produced by the enzyme-enhanced chemistry which allows multiple readings to be taken, for precise measurements.

The rapid detection times and very low background make the chemiluminescent methods faster than RIA or other EIA methods. Chemiluminescent immunoassays have achieved levels of sensitivity several orders of magnitude better than RIA and fluorometric immunoassays.
ACMIA: Affinity Chrome-Mediated Immunoassay. ACMIA is a technique to measure drug concentrations in which free and drug-bound antibody-enzyme conjugates are separated using magnetic (chrome) particles. Sample is mixed with the antibody-enzyme conjugate. Analyte (drug) present in the sample is bound by the antibody conjugate reagent. Magnetic particles coated with the analyte are added to bind free antibody-enzyme conjugate. The reaction mixture is then separated magnetically. Following separation, the supernatant containing the analyte-antibody-enzyme complex is transferred by the instrument to another cuvette and mixed with a substrate. B-galactosidase catalyzes the hydrolysis of CPRG (chloropenol red B-galactopyranoside) to produce CPR (chloropenol red) that absorbs light at 577 nm. The change at 577 nm due to the formation of CPR is directly proportional to the amount of analyte present in the sample, and is measured by a bichromatic (577, 700 nm) rate technique.

CEDIA: Cloned Enzyme Donor Immunoassay. CEDIA employs a recombinant DNA technology. The technique is based on the bacterial enzyme B-galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociate to form fully active enzymes that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotometrically. Analyte in the sample competes with analyte conjugated to one inactive B-galactosidase fragment for antibody binding sites. If analyte is present, it binds to antibody, leaving the inactive enzyme fragments free to form active enzyme. If analyte is not present, antibody binds to analyte conjugated to inactive fragment, inhibiting reassociation of these inactive B-galactosidase fragments and no enzyme is formed. The amount of active enzyme formed (absorbance change) are directly proportional to the amount of analyte present in the sample.

Summary
The type of immunoassay methods used in TDM testing include HPLC, GC/MS, LC/MS, RIA, PETINIA, EIA, FPIA, EMIT, ACMIA, CEDIA and direct chemiluminescence. Early TDM technologies were labor intensive, expensive, and required specialty operators who turned around assay results much slower than today. These technologies have evolved over the past several decades to provide automated, less labor intensive, better sensitivity and specificity, more reliable and faster turn around results.
### Appendix

#### Antiepileptics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol, Carbatrol)</td>
<td>Used to treat psychomotor seizures, tonic-clonic seizures, and mixed seizures. Often given with phenytoin. Also used to treat trigeminal and glossopharyngeal neuralgia pain. May be used for bipolar disorder when lithium is not effective.</td>
<td>4 – 10 µg/mL</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Effective means of preventing absence (petit mal) seizures.</td>
<td>10 – 150 µg/mL</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Effective therapy for tonic-clonic seizures, temporal lobe seizures and neonatal seizures.</td>
<td>15 – 40 µg/mL</td>
</tr>
<tr>
<td>Primidone</td>
<td>Monitoring serum Primidone concentrations is the most effective means of improving seizure control and reducing the risk of toxicity.</td>
<td>2.5 – 20 µg/mL</td>
</tr>
<tr>
<td>Valproic Acid (Depakene)</td>
<td>Used to treat petit mal, tonic-clonic, and myoclonic seizures. Monitoring this drug is important because its pharmacokinetics are unpredictable.</td>
<td>50 – 100 µg/mL</td>
</tr>
</tbody>
</table>

#### Antiarhythmics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitoxin (Crystodigin)</td>
<td>Used to improve cardiac contraction in congestive heart failure and to correct supraventricular tachycardia.</td>
<td>10 – 30 ng/mL</td>
</tr>
<tr>
<td>Digoxin (Lanoxin, Digitek)</td>
<td>Used to improve cardiac contraction in congestive heart failure and to correct supraventricular tachycardia.</td>
<td>0.9 – 2 ng/dL</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Antiarhythmic</td>
<td>1 – 30 µg/mL</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Monitoring lidocaine in serum during infusions helps to establish and maintain adequate prophylactic or therapeutic drug concentrations and avoid toxicity.</td>
<td>1.5 – 5 µg/mL</td>
</tr>
<tr>
<td>NAPA</td>
<td>Measurement of N-acetylprocainamide, together with procainamide concentrations helps to achieve an optimum antiarhythmic effect and reduce the risk of toxicity.</td>
<td>10 – 30 µg/mL</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Monitoring serum procainamide concentrations helps to achieve an optimum antiarhythmic effect and reduce the risk of toxicity.</td>
<td>4 – 12 µg/mL</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Monitoring serum quinidine concentrations, along with clinical assessment, is the most effective means of achieving an optimum antiarhythmic effect and reducing the risk of toxicity.</td>
<td>0.5 – 8 µg/mL</td>
</tr>
</tbody>
</table>

#### Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Used to treat different types of bacterial infections. Most often used to treat severe infections with multidrug resistant Gram negative bacteria.</td>
<td>Peak:* 15 – 30 µg/mL</td>
</tr>
<tr>
<td>Gentamicin (Garamycin)</td>
<td>An aminoglycoside antibiotic used to treat life-threatening gram-negative infections. Excess dosage can cause kidney and auditory nerve damage.</td>
<td>Peak: 5 – 10 µg/mL</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>Used to treat serious infections, particularly those resistant to gentamicin.</td>
<td>Peak: 1 – 12 µg/mL</td>
</tr>
<tr>
<td>Tobramycin (Nebcin, Tobi, Tobrex)</td>
<td>An aminoglycoside antibiotic used to treat Gram-negative infections such as Pseudomonas aeruginosa.</td>
<td>Peak: 5 – 10 µg/mL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Inhibits protein synthesis of the bacterial cell wall. Most commonly prescribed for gram-positive cocci infections such as Staphylococcus aureus.</td>
<td>Peak: 30 – 40 µg/mL</td>
</tr>
</tbody>
</table>

#### Antineoplastics

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Monitoring methotrexate concentrations and rate of decline in serum during high-dose therapy is essential when designing adequate tocopherol rescue dosages.</td>
<td>0.1 – 2600 µmol/L</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Newborns with apnea may be treated with Theophylline, which is metabolized to Caffeine in their immature metabolism, or directly with caffeine. Monitoring of caffeine levels in serum or saliva is recommended.</td>
<td>1 – 30 µg/mL</td>
</tr>
<tr>
<td>Theophylline (Theo-Dur, Bronkodyl)</td>
<td>A respiratory stimulant, it is used to relax smooth muscles in bronchi and pulmonary blood vessels in asthma, neonatal apnea, and acute pulmonary edema.</td>
<td>10 – 20 µg/mL</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Suppresses the function of the immune system. Drug of choice following organ transplantation. Has decreased the rate of organ rejection. High doses can result in liver and renal failure.</td>
<td>50 – 350 µg/mL</td>
</tr>
<tr>
<td>Everolimus (Certican)</td>
<td>Aids in the function of suppressing the immune system. Decreases the rate of organ rejection, especially for kidney transplant patients.</td>
<td>3 – 8 µg/mL</td>
</tr>
<tr>
<td>Mycophenolic Acid</td>
<td>Aids in the function of suppressing the immune system. Decreases the rate of organ rejection, is used as combination medication in the majority of transplantation patients.</td>
<td>1 – 4 µg/mL</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>Aids in the function of suppressing the immune system. Decreases the rate of organ rejection, especially for kidney transplant patients.</td>
<td>3 – 15 µg/mL</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Suppresses the function of the immune system. Decreases the rate of organ rejection, especially for kidney transplant patients.</td>
<td>3 – 15 µg/mL</td>
</tr>
</tbody>
</table>

*recommended concentrations can vary depending on the infection/severity.
Absorption – The transition of drug from the site of administration to the blood circulation.

Aminoglycoside – A group of injectable antibiotics active against a wide range of bacteria.

Bioavailability – A measure of how much of the drug makes it into the bloodstream and becomes available to the target tissue.

Cmax – The maximum concentration of drug in the blood.

Cmin – The minimum concentration of drug in the blood.

Distribution – The transition of drug from the blood circulation to the target tissue(s).

Dosage Regimen – The complete description of drug administration, includes dose rate and interval.

Elimination – Removal or transformation of a drug in circulation, usually via the kidney and liver. Many factors affect a drug’s elimination rate including hepatic and renal function, age, disease, protein binding, etc.

Elimination Half-Life – Time required for the amount of drug in the body to decrease by 50%.

Excretion – Elimination of a drug via renal, biliary, or pulmonary processes.

First Pass Loss – Removal of a fraction of drug dose by the liver before it reaches the systemic circulation.

Half-life – A measurement of how long a drug stays in the blood.

Loading Dose – Dose(s) of drugs given at the onset of therapy to rapidly provide a therapeutic effect. Use of a loading dose prior to a maintenance dosage regimen will shorten the time required to approach a steady state.

Maintenance Dose – A dosing regimen designed for chronic therapy.

Metabolism – The conversion of a drug from the circulating blood to the target tissue(s).

Peak Serum Concentration – The highest serum drug concentration that occurs following a single dose or at steady state within a dosing interval. Determining the exact peak requires numerous serial blood samples.

Pharmacokinetics – The study of how drug levels change over time in the body.

Protein binding – Serum proteins function as carriers for many drugs, hormones, etc and transport the substances around the body in the bloodstream. Only the unbound or free fraction is available to act on the target tissues.

Steady State – Represents the equilibrium between the amount of drug given and the amount eliminated over the dosing interval. In general it takes a drug four to five half-lives to reach a steady state. Sampling should occur when the drug has reached its steady state to judge efficacy and toxicity of the drug therapy. Steady state should not be confused with the therapeutic range.

Steady State Concentration – Serum drug or metabolite concentrations during a dosing interval after a steady state has been achieved. Steady state concentrations fluctuate between a maximum (peak) and minimum (trough) concentration with each dosing interval.

Therapeutic Range – Range of drug concentrations associated with high degree of efficacy and low risk of dose-related toxicity in majority of patients.

Trough Serum Concentration – The lowest drug concentration during a dosing interval when drug is given intermittently. The trough concentration generally occurs immediately before administration of the next dose.

Total Drug Concentration – The sum of unbound and bound drug in serum or plasma.

Unbound Drug Concentration – The concentration of drug in serum and plasma that is free and not bound to proteins. The unbound drug concentration in serum is more closely associated with drug response than total drug concentrations.


Siemens Healthcare Diagnostics
Therapeutic Drug Monitoring Test Menu

- Amikacin
- Caffeine
- Carbamazepine
- Cyclosporine
- Digitoxin
- Digoxin
- Disopyramide
- Ethosuximide
- Gentamicin
- Lidocaine
- Methotrexate
- Mycophenolic Acid
- NAPA
- Phenobarbital
- Phenytoin
- Primidone
- Procainamide
- Quinidine
- Sirolimus
- Tacrolimus
- Theophylline
- Tobramycin
- Valproic Acid
- Vancomycin

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