Therapeutic Drug Monitoring Course

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I- Introduction

Therapeutic drug monitoring and pharmacogenomics are both clinical toxicology-related areas within the clinical laboratory. Although each is considered a sub-discipline within laboratory medicine, the two fields overlap significantly. This course provides an overview of each of these laboratory sub-disciplines and discusses the utility, rationale, and practice of each one. The course is intended for clinical toxicologist, clinical laboratory health care personnel and other technologists and technicians who are responsible for monitoring, prescribing and administering therapeutic medications.

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Albuterol is a fast-acting bronchodilator used acutely during asthma attacks. Which of the reasons below explains why TDM for albuterol is not availab...
III- Course content

Introduction

Therapeutic drug monitoring and pharmacogenomics are both clinical toxicology-related areas within the clinical laboratory. Although each is considered a sub-discipline within laboratory medicine, the two fields overlap significantly. In this course, we will provide an overview of each of these laboratory sub-disciplines and discuss the utility, rationale, and practice of each one.

Therapeutic Drug Monitoring Definition

Therapeutic Drug Monitoring (TDM) is a branch of clinical chemistry that specializes in the measurement of medication levels in serum. TDM requires that the laboratory make quantitative measurements of drugs and/or their metabolites. These measurements are almost always made on patient serum samples. TDM can be contrasted with urine drug testing. Urine drug testing is usually performed to detect or monitor drug abuse or check patient compliance when a drug with high abuse potential has been prescribed. Determining actual concentrations are less important for urine drugs of abuse screening. Provided accurate concentrations for TDM, on the other hand, is essential. Serum concentrations provided with TDM allow clinicians to adjust medication dosages as well as assess a patient’s drug metabolism response and their compliance or dosing regimen.

Pharmacogenomics Definition

Pharmacogenomics (usually abbreviated PGx) is the study of how variations in the human genome affect a given individual’s response to medications. It refers to how administered drugs will be handled by a specific person given specific genetic mutations and polymorphisms they may have.

Basic Pharmacokinetics

In order to discuss TDM and PGx we need to also introduce the concept of pharmacokinetics. Pharmacokinetics is the study of drug disposition in the body: It concerns how and when drugs enter the circulation, how long they remain in the blood, and how they are ultimately eliminated from the body. TDM is the clinical assessment of a drug’s pharmacokinetic properties. Physicians and clinical toxicologist, pharmacists often need to establish that a drug is present at a clinically-effective concentration yet does not reach a toxic concentration. The next few pages will describe some of the factors that determine a drug’s disposition in the body. These factors ultimately decide the need for therapeutic drug monitoring.
Drug Concentration Over Time

When a drug enters the body, it reaches a peak concentration that starts to fall as the drug is eliminated. The figure on the right shows a typical drug kinetic when a drug is given intravenously (IV).

Drug Metabolism

The liver plays a major role in converting lipophilic, nonpolar molecules (including drugs) to more polar, water-soluble forms through a series of enzymatic reactions. Drug molecules can be modified by either phase I or phase II reactions. These reactions are carried out by several important classes of enzymes.
- Phase I reactions alter chemical structure by oxidation, reduction, or hydrolysis.
- Phase II reactions conjugate drugs to create products that are water-soluble.

Drug Elimination

Most water-soluble drugs are eliminated from the body through hepatic metabolism, renal filtration, or a combination of the two. It makes sense that the body would aim to make a drug water soluble. When a small molecular-weight compound is water soluble, it can be excreted from the blood by simple filtration through the kidneys and it will then enter the urine. Since fatty, nonpolar molecules do not dissolve in water they tend to accumulate in tissues or bind strongly to proteins. Until the body can render these molecules water-soluble, they are much less likely to be excreted.

An alteration in renal function will have a major effect on the clearance of the drug or its active metabolite(s). Decreased renal function results in elevated serum drug concentrations.

Half-life

The amount of time it takes for a drug concentration in the body to decrease by 50% is called the drug’s half-life (abbreviated t1/2). The longer a drug’s half-life, the slower it is removed from the body. Most drugs are eliminated from the body in 1 to 3 days, but some drugs with longer half-lives can still be detected in the body weeks after the initial dose. The figure below illustrates a typical kinetic pattern for an oral drug.
Bioavailability

Bioavailability refers to the amount of drug that actually reaches the circulation. It is calculated by comparing (in the same subjects) the area of the curve (AUC) that is found under the serum concentration kinetic graph. This is done using an equivalent dose of the intravenous form and oral form. Then the two areas are compared. This is illustrated in the diagram on the right. The fraction of oral drug that makes it to the circulatory system is the bioavailability of that drug. For IV drugs, the bioavailability is 100%.

For oral medications, the bioavailability will be less than 100%, due in part to any of these reasons: 1- Oral drugs have slower absorption and distribution than IV drugs. 2- The amount of drug that is absorbed can depend on the status of the GI tract (stomach pH, presence of food, integrity/health of the intestines, speed of the GI tract, etc.). Oral drugs may be broken down by enzymes that are present anywhere along the GI tract.

If bioavailability is low then the oral dose needed has to be increased so that a given dose achieves the appropriate serum concentration. Since the absorption of an oral drug is slower than an IV drug and the drug takes longer to enter the circulation, clearing the drug will also most likely take a longer time.

![Diagram of Bioavailability and AUC comparison](image)

Protein Binding

Most drugs are bound to proteins when they circulate in the body. This makes sense when considering general solubility rules of chemistry. If a drug is simple, eg, an elemental salt such as lithium, it will easily dissolve into the aqueous environment of the blood and widely distribute through the circulation. However most drugs are complex organic molecules with variable solubility in water. For drugs that are not highly soluble in an aqueous environment, some carrier protein will be needed to solubilize that drug into blood. Serum contains a myriad of proteins.

Although these proteins themselves are water soluble (since they are found dissolved in blood) they often contain lipophilic regions on them, which can bind non-polar drugs and thus carry these drugs through the circulation.

![Diagram of Drug Binding to Proteins](image)
Albumin is a major drug-binding protein in serum. Albumin is an alkaline protein, so acidic and neutral drugs primarily bind to it. If albumin binding sites become saturated, acidic and neutral drugs can bind to lipoproteins. Alkaline drugs tend to bind to globulins, particularly to a globulin called alpha-1 acid glycoprotein. Only free, unbound drugs are able to bind protein drug receptors on cells and have therapeutic effects.

An equilibrium exists in the systemic circulation between a free and protein-bound drug and between a free and receptor-bound drug. This is illustrated in the image to the right.

### Protein Availability and Drug Dosing

Drug-binding proteins in serum can fluctuate in disease states. For example, if albumin levels fall, as can occur in liver failure or nephritic syndrome, less albumin will be available for drug binding. If this happens a new dose of drug may produce a toxic concentration of free drug since albumin is now lower. The image on the right illustrates the loss of equilibrium between a protein-bound drug and a free drug when drug-binding proteins are diminished. Doses of drugs that are highly protein-bound may need to be adjusted in patients with lower drug-binding protein levels. Examples of some common drugs that are highly protein-bound include thyroxine, warfarin, diazepam, heparin, imipramine and phenytoin.

![Diagram showing equilibrium between protein-bound and free drugs](image)

**Conclusion:** So far we have learned that many factors (protein binding, lipophilicity, bioavailability, elimination, etc.) affect a drug’s disposition in the body. Because we usually cannot safely predict how a drug will be tolerated in a person, we use therapeutic drug monitoring (TDM) to verify that a drug is present at an appropriate concentration.

### Other Factors Affecting Drug Absorption and Distribution

In addition to protein availability, other factors may affect drug absorption and distribution in the body as a whole or within specific sites of the body. The following table highlights some of these other factors.
Reduced area blood flow can be seen in diabetics and enhanced blood flow can be seen in tumors. Reduced blood flow means reduced exposure to drug.

The more lipophilic a drug is, the more likely it will enter the central nervous system. The brain itself is a very lipid rich organ but there also exists a tighter-than-normal web of epithelial cells in the CNS blood vessels. This leads to the so called blood-brain-barrier. Lipophilic drugs can cross cell membranes of this barrier more easily than polar drugs.

In a diseased gut, an orally-administered drug may not be absorbed as expected.

Drug kinetics and dispositions change throughout life. In general, metabolism of drugs is reduced in the elderly.

Mutations or deletions in drug metabolizing enzymes can greatly affect a drug’s disposition.

Most drugs are not given as a single dose but are part of a multi dose regimen. It is the physician’s responsibility to prescribe a drug such that the concentration of that drug reaches a safe and effective level as quickly as possible without inducing toxicity. The dosing-goal for the prescribing clinician, if multiple doses of a drug will be given, is for both the peak and the trough drug levels to be consistently within the therapeutic range. If a drug is given at intervals that are the same as its half-life, it will take about 5 half-lives to reach steady state.

If the drug Gentamicin has an elimination half-life of 12 hours and is given every 12 hours, the drug should reach steady state after 5 half-lives (60 hours). Notice in the diagram that this kind of dosing results in a ‘sawtooth’ pattern. Peaks correspond to the times right after the drug is taken; troughs correspond to the times right before the next dose.

Of course a physician may want to get a patient into the therapeutic range more quickly. In these cases a higher loading dose of drug can be prescribed initially with instructions that after the first couple of doses, the dose should be reduced.
Sampling

Ideally, a drug level would be monitored frequently and consistently, providing the clinician with a detailed pharmacokinetic profile over time. In reality, serum samples are often measured only during relatively infrequent clinic visits, meaning that many days or weeks may pass before a drug concentration ‘snap-shot’ is taken. This then requires us to ask: ‘when should we collect blood in order to best measure the serum concentration of the drug in question?’

Peak and Trough Sampling Times

A trough refers to the valley or bottom ‘spike’ of the sawtooth pattern we saw earlier. When a drug is taken orally the trough will be the low point of the serum concentration. It will be the time period immediately before the next dose. Thus, when we want to draw a trough level we draw just before the patient is supposed to take their next dose. To assess peak levels (the time of maximum concentration) the time for drawing depends on the route of administration and the absorption kinetics of the drug.

For oral medications One hour after drug is taken is usually adequate (this assumes a half-life of > two hours). For IV medications: sample 15-30 minutes after injection/infusion. For Intramuscular (IM) injections: sample 30 minutes to one hour after injection.
Why Therapeutic Drug Monitoring TDM?

Pharmacologists determine a drug's pharmacokinetic characteristics empirically during clinical drug trials. From these studies, they are able to determine the solubility and distribution, the average half-life, the levels of protein binding, and the effective concentrations needed for treatment.

However, every patient is unique. Changes in the gut (if the drug is taken orally), genetic variations in the liver's metabolizing enzymes, and the functional status of organs (like the kidneys and liver) all affect how a drug will be handled by an individual. Given these variables, it becomes important to take a measurement of the drug in serum so that we can be sure the dose given is leading to an appropriate concentration in the body. TDM helps to ensure that a dosing regimen is appropriate for a given patient.

Every drug has a sub-clinical concentration (a concentration at which effective therapy won't be achieved) and a toxic concentration (a concentration at which the drug will be harmful to the patient.)

For some drugs, the range between the minimum effective concentration and the toxic concentration is large. These drugs are thus relatively safe. Other drugs have a very narrow therapeutic window and need closer monitoring. This is the role of TDM. Medications with narrow therapeutic windows, like the anticonvulsant carbamazepine (Tegretol), should be closely monitored since elevated doses can cause serious conditions such as agranulocytosis.
**Unexpected Concentrations:**

TDM provides a quantitative measure of the circulating concentration of a drug. The physician determines if the dosage of the drug needs to be adjusted based on this information.

If a drug concentration is determined to be outside the therapeutic range, it may be for one of the reasons listed in the table below.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncompliance</td>
<td>Patients may (intentionally or unintentionally) not take the drug as prescribed. TDM can thus help monitor compliance.</td>
</tr>
<tr>
<td>Dosing errors</td>
<td>The dose may have been erroneous or inappropriate given the patient's condition.</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>The TDM result will reveal if the drug cannot be absorbed well through the gut and an alternative route of administration will be needed.</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many drugs interfere with the absorption or metabolism of other drugs. These interactions will be revealed by TDM.</td>
</tr>
<tr>
<td>Kidney or liver disease</td>
<td>Any pathology that affects elimination will cause an elevation in a drug level that will be unmasked by TDM.</td>
</tr>
<tr>
<td>Altered protein binding</td>
<td>Mutations or deletions in drug metabolizing enzymes can greatly affect a drug's disposition.</td>
</tr>
</tbody>
</table>

Variations in the genetics of drug-metabolizing enzymes can also affect drug concentrations in the body. This is the field of pharmacogenomics that will be discussed later in the course.

**Conclusion:** The drug should be measured at a time corresponding to the peak concentration (not the trough). One to 2 hours after an oral dose is usually sufficient time for a drug to be absorbed and should correspond to peak concentration. A drug measurement that is taken 2 to 4 hours after an IV injection of the drug will not represent the peak value. A drug that is given via IV enters the circulation immediately, and the peak concentration of the drug would be measured 15 to 30 minutes after the IV injection. A measurement that is taken just before the next dose is given represents the trough value of the drug.

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TDM For All Drugs?

Can all drugs benefit from TDM? Not really. For TDM to be effective and useful, one or more of the following should apply:

- The effective concentration and toxic concentrations must be well-defined.
- The pharmacokinetics of the drug are known to be variable.
- The drug is given chronically.
- There is the potential for drug-to-drug interactions.
- The drug exhibits high protein binding.
- The toxicity will mimic the indication for the drug; toxicity may not be visible during an exam but will only be revealed with TDM.
- The patient is pregnant, very young, or elderly.
- Compliance or history with the drug is poor.

Unless criteria like these exist, it doesn't make much sense to perform TDM testing. Penicillin, for example is never measured in the serum. It has a wide therapeutic window, it is not given chronically, it has minimal toxicity, etc.

When is TDM Not Useful?

TDM is not useful in these specific situations:

- For drugs which act intracellularly, or that need to be converted to active forms (like AZT)
- For drugs in which the effects last much longer than the serum concentrations of the drugs; examples include Antineoplastics (cancer chemotherapies) and warfarin.
- Narcotic pain medications where continued use can lead to tolerance such that the levels needed for pain relief in one person would be toxic to another person.

Alternative to TDM

Some drugs are more efficiently monitored by determining their effects rather than by measuring the serum drug level. Warfarin dosing, for example, is better monitored by measuring the prothrombin time (PT) and International Normalized Ratio (INR). We monitor warfarin by looking at the physiologic effect since the effects of warfarin will outlast its presence in the blood.
Examples of Drugs That are Monitored by TDM

Four major classes of drugs are frequently monitored by TDM:

1. Antibiotics
2. Anticonvulsants
3. Immunosuppressants
4. Cardiac medications

There are other drugs that are monitored by TDM that are not included in any of the above classifications, but the majority of TDM testing is performed for drugs that are included in one of these four categories.

TDM for Antibiotics

Infection is obviously a very serious indication, and effective antibiotic levels must be achieved as soon as possible. However, many antibiotics also have nephrotoxic or ototoxic effects; the concentrations of these antibiotics need to be monitored. Having serum concentrations too low or too high are both situations which must be avoided.

Examples of antibiotics that are monitored by TDM include:

- Amikacin
- Gentamicin
- Tobramycin
- Vancomycin

Antibiotics such as ampicillin that are readily cleared and have a wide therapeutic window are not usually monitored by TDM.

TDM for Anticonvulsants

Anticonvulsants (also known as anti-epileptic or anti-seizure medications) typically have narrow therapeutic windows. When levels are too low, the risk for seizure remains present. Drug levels that are too high can depress the central nervous system and may even lead to coma.

Examples of anticonvulsants that are monitored by TDM include:

- Carbamazepine (Tegretol)
- Valproic acid (Depakene)
- Phenytoin (Dilantin)
- Phenobarbital
- Primidone (Mysoline)

TDM for Immunosuppressants

Drugs used to inhibit the immune system are part of standard treatment after transplant surgeries. Unfortunately, these life-saving drugs also cause hepatotoxicity and nephrotoxicity with high concentrations. The reason drug monitoring is used for immunosuppressants is to ensure that concentrations are adequate to suppress the immune response and prevent rejection yet not high enough to cause liver failure or severe immunodeficiency.

Examples of immunosuppressants that are monitored by TDM include:

- Cyclosporine
- Methotrexate (this drug is also used as an anti-neoplastic drug)
- Tacrolimus
- Sirolimus

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TDM for Cardiac Medications

Inotropics (drugs used to increase the pumping ability of the heart) and antiarrhythmics may need TDM. The cardiac glycoside inotropics digoxin and digitoxin have narrow therapeutic windows. Overdose can cause vomiting, diarrhea, confusion, visual disturbances, and cardiac arrhythmias. A difficulty with these medications is that overdose produces the same symptoms that the drug is used to treat. For example, procainamide is used for arrhythmia, but an overdose of procainamide can produce an arrhythmia. Thus, without TDM the physician will not know whether to give more drug or less, since both states can lead to the same presentation.

Examples of cardiac medications that are monitored by TDM include:
- Digoxin
- Digitoxin
- Procainamide
- N-Acetylprocainamide (NAPA) -the metabolite of procainamide
- Quinidine

TDM for Theophylline

Theophylline is used as a bronchodilator for the treatment of moderate to severe asthma and chronic obstructive pulmonary disease (COPD).

TDM is needed for theophylline because the kinetics of the drug are highly variable. It has a narrow therapeutic window, and overdose can result in elevated heart rate, arrhythmia, and CNS excitability.

Clearance of the drug is increased in children, smokers, persons with cystic fibrosis, and persons with hyperthyroidism. Elimination is slowed in congestive heart failure and in the elderly.

Laboratory Methods

Immunosassays are the most common technique used by clinical laboratories for therapeutic drug monitoring. Antibodies that recognize specific drugs have been developed. Although most drugs are much too small to evoke an immune response, scientists can conjugate drugs to immunogenic proteins to produce antibodies that recognize drug-specific epitopes.

There are several methods that utilize the principals of immunoassay for detection and quantification of therapeutic drugs in serum.

Some of these methods are:
- Particle-enhanced turbidimetric inhibition immunoassay (PETINIA)
- Cloned enzyme donor immunoasssay (CEDIA)
- Fluorescence Polarization Immunoassay (FPIA)
- Chemiluminescent assays

PETINIA

Particle-enhanced turbidimetric inhibition immunoassay (PETINIA) is a homogeneous competitive immunoassay.

Antibody fragments and drug-lab particles will bind to form aggregates that increase the turbidity of the solution. Free drug from the sample competes for the antibody fragment, thereby decreasing the rate of particle aggregation.

The rate of aggregation is inversely proportional to the concentration of drug in the sample.
Fluorescence polarization immunoassay (FPIA) is also a homogenous competitive immunoassay. In this system, fluorescein-labeled drug competes with unlabeled drug from the patient's serum sample for binding sites on an antibody reagent.

The patient's sample, presumably containing the therapeutic drug that is being monitored, and the fluorescein-labeled drug are added to a chamber containing antibody for that drug.

The labeled and unlabeled drug will compete for binding sites on the antibody. The greater the amount of drug in the sample, the fewer the number of binding sites that are available for the labeled analyte, leaving a greater number of small, free fluorescein-labeled molecules in the solution.

When the chamber is excited with plane polarized light, fluorescein will absorb the light and emit it at a higher wavelength as fluorescent light.

A small, free fluorescein-labeled drug rotates randomly and faster than it would if it were bound to antibody, interrupting the light and leading to less emission of light.

The larger antibody-drug-fluorescein complexes rotate slower and emit more light in the measured plane.

A lower level of drug in the patient's sample results in greater emission of polarized light because there are more antibody-drug-fluorescein complexes present to produce light in the measured plane. A higher level of drug in the patient's sample results in a lower emission of polarized light. This inverse relationship between the concentration of the drug and the polarization units (signal) is illustrated in the image below.

FPIA assays are rapidly being replaced by higher-throughput chemiluminescent assays. FPIA is now rarely used.

Chemiluminescence

Chemiluminescent assays use antibodies that are conjugated to enzymes, such as peroxidase or alkaline phosphatase. These enzymes, when mixed with chemiluminescent substrates, produce light in the visible spectrum.

A direct relationship exists between the amount of drug that is present in the sample and the light units that are produced and measured by the luminometer in the instrument. Assays that use chemiluminescence are more sensitive than immunoassays that rely on the generation of a colored product.
**Individualized Medicine**

It has been said that we live in a new era of "individualized medicine" or "personalized medicine." One of the primary drivers for this idea is the emerging field of pharmacogenomics (PGx). PGx is the study of how individual variations in the human genome affect responses to medications.

The term "pharmacogenetics" is also used for this discipline (people in the field use both terms; however, the term 'pharmacogenomics' is more popular).

The primary reason that individuals metabolize and respond to drugs differently is the individual differences in receptor proteins and enzymes that metabolize the drugs. Mutations in these receptor proteins and enzymes can give rise to very different responses to drugs. In PGx, these mutations are referred to as variants.

**Polymorphism and CYP450**

To discuss PGx, we must first define two terms:

1. A polymorphism is a variation in a specific gene (allele) that affects at least 1% of the population. It is essentially a mutation that occurs relatively frequently in the population.
2. CYP450 refers to a family of enzymes found predominantly in the liver. CYP450 enzymes work on a variety of substrates (in this case, drugs), altering their chemical structures to facilitate excretion in the urine and feces.

There are many known polymorphisms which occur in the protein sequences of CYP450 enzymes.

**CYP450s**

Many CYP450 enzymes have been characterized, and the substrates (drugs) that each can recognize have been worked out to a large extent. The major subfamilies of CYP450 enzymes that have to-date, been associated with significant polymorphisms that affect drug disposition are:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6

**CYP2D6**

There has been much research on CYP450 enzymes and many papers reporting polymorphisms with clinical significance. We can't discuss all CYP450s but lets consider CYP2D6 as an example:

- It is estimated that about 25% of common drugs are metabolized by CYP2D6.
- CYP2D6 accounts for only about 1% of all CYP450 enzymes, but it is important in the metabolism of about 100 drugs.
- There are more than 80 genetic variants that have been described in the CYP2D6 gene. The normal, wild-type allele displays normal metabolic activity whereas some of the variant forms have enhanced or diminished activity.
- The variants can be grouped generally according to the resulting alterations in protein function.
- The groupings correlate with four major enzyme metabolic capacities (phenotypes): poor, intermediate, extensive (normal), or ultrarapid metabolizers.
Metabolizers

When discussing PGx, we classify a person according to his/her phenotype (their metabolic capacity for a given enzyme).

- A poor metabolizer (PM) is a person who lacks a fully-functional enzyme or has reduced expression of the enzyme and therefore exhibits decreased metabolism of drugs. This person would require lower doses of a drug that is metabolized by that enzyme. A PM who receives a standard dose is more likely to experience unwanted side effects or toxicity. A PM can also experience diminished effects with drugs that need to be metabolized to active compounds by the enzyme in question.

- An ultrarapid metabolizer (UM) will require a higher dose than usual since he/she has a polymorphism (mutation) that codes for a more efficient enzyme or more expression of an enzyme. They will eliminate the drug more quickly. A UM may be resistant to standard treatments, and it may take some time to adjust the dosage before therapy is achieved.

- An intermediate metabolizer (IM) has one wild-type (normal) copy of the gene and one absent or dysfunctional copy. The IM group is very heterogeneous.

- A person with normal enzyme activity is referred to as wild type or as an extensive metabolizer (EM). This person should respond to standard dosages of a drug. Most people are EM's. This is the population in which most dosing regimens have been worked out in clinical trials.

Enzyme Abnormalities and Drugs

Not all PGx is concerned with CYP450 enzymes. There are other drug-metabolizing enzymes that show polymorphisms and can affect the way people respond to a drug. The following is a list of enzymes for which known mutations have been associated with clinical effects.

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Substrates (Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>Succinylcholine</td>
</tr>
<tr>
<td>Alcohol dehydrogenase</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Dihydropyrimidine dehydrogenase</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin, phenytoin, losartan</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Diazepam, omeprazole (Prilosec)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Many antidepressants, opioids, antiarrhythmic</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>Aspirin, quinidine</td>
</tr>
<tr>
<td>N-acetyltransferase</td>
<td>Procainamide, isoniazid</td>
</tr>
<tr>
<td>Thioprine methyltransferase</td>
<td>6-mercaptopurine</td>
</tr>
<tr>
<td>UDP-glucuronosyl transferase</td>
<td>Acetaminophen, tolbutamide, irinotecan</td>
</tr>
</tbody>
</table>

Clinical Utility

- The ultimate goal in measuring CYP450 function or identifying polymorphisms is to predict effective therapeutic doses and responses in patients.

- Polymorphisms are identified using molecular techniques (allele-specific PCR, restriction digests, sequencing, hybridization assays, bead-based systems, microarrays, pyrosequencing, et al).
• Although most clinical labs do not offer PGx testing, reference labs are beginning to market these tests. For example, one reference laboratory in the Midwest that offers CYP2D6 profiling measures about one dozen of the most common and significant mutation sites on this enzyme. This allows for detection of approximately 98% of the known CYP2D6 polymorphisms. The laboratory then generates a report which will advise the physician on the patient's drug-metabolizing status.

• Estimates show that 6-10% of the general population have a complete deficiency of CYP2D6, with the prevalence of mutations varying from <1% to as much as 21% within a given population.

### Warfarin Metabolism

• PGx testing for warfarin metabolism has received the most attention thus far.

• Recent studies have revealed that about half of the variations seen in patients taking the anticoagulant warfarin are due to PGx factors. The consequences of incorrect warfarin dosing are obviously serious, with inadequate doses predisposing patients to thrombosis and higher doses placing them at risk for hemorrhage.

• The United States’ Food and Drug Administration (FDA) recently approved updated labeling for Coumadin (warfarin sold by Bristol-Myers Squibb). The new labeling suggests that physicians incorporate PGx information into warfarin-dosing regimens for patients. Manufacturers of generic warfarin products are now adding similar labeling.

• The genes involved in warfarin metabolism are CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKOR).

• Warfarin owes its anticoagulant action to its inhibition of VKOR. This enzyme recycles vitamin K, a critical element for the clotting. There are six CYP2C9 alleles that are known to cause prolonged metabolism of warfarin: CYP2C9 *2, *3, *4, *5, *6, and *11. (Polymorphisms in CYP450 genes are denoted with asterisks.)

• One-third of the patients that receive warfarin metabolize it differently than expected and experience a higher risk of bleeding.

• Genetic testing for the two most common polymorphisms (CYP2C9*2 and *3) as well as for VKOR may be able to reduce the variability associated with warfarin dosing response.

• Labs performing PGx testing can provide general warfarin dosing recommendations based on the patient’s genotype analysis. The lab report will indicate whether a patient has a normal, mild, moderate, high, or very high sensitivity to warfarin. Online calculators or handy paper charts can then help physicians calculate an appropriate starting and maintenance dose given the phenotype of a particular person.

• For example, a patient who has one CYP2C9 normal wild-type allele (CYP2C9 *1), one polymorphism (CYP2C9*3), and also a VKOR polymorphism is predicted to have a moderate sensitivity to warfarin. This patient should have frequent INR monitoring and possible warfarin dose reduction.

• It is important to recognize that knowing a genotype does not necessarily guarantee accurate dose prediction; other drugs and/or environmental or disease factors can also alter CYP2C9 activity. Therefore, monitoring the INR is still very important.

**Conclusion:** A person classified as an ultrarapid metabolizer (UM) has a polymorphism that enhances the catabolic activity of the enzyme. This means that a UM would need more of the drug to achieve a 'normal' level since he/she is rapidly metabolizing the drug.
CYP450 Induction and Inhibition

- PGx is not the only factor to consider when thinking about variation in drug responses among different people. Although polymorphisms of drug-metabolizing enzymes are a big player, there are other big players that influence drug metabolism.
- For example, many drugs are able to induce the expression of CYP450 enzymes (cause cells to produce more of a particular enzyme). Also, CYP450s can be inhibited by a variety of substances. For example, CYP2D6 can be inhibited by the common medications cimetidine (Tagamet) and fluoxetine (Prozac). Substances in food can also affect CYP450 expression or may simply compete with a drug for metabolism. An example is grapefruit. Several organic compounds found in grapefruit have an inhibitory action on CYP3A4.
- Since many patients are on multiple medications and since dietary and environmental factors can change, CYP450 expression levels cannot be solely predicted based on their genotype.
- Some CYP450 inducers and inhibitors are listed in the table on the following page.

<table>
<thead>
<tr>
<th>CYP450</th>
<th>Inhibitor</th>
<th>Inducer</th>
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<tbody>
<tr>
<td>CYP1A2</td>
<td>Amiodarone</td>
<td>Tobacco</td>
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<td></td>
<td>Cimetidine</td>
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<td></td>
<td>Ciprofloxacin</td>
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<td>CYP2C9</td>
<td>Amiodarone</td>
<td>Rifampin</td>
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<td></td>
<td>Fluvasatin</td>
<td>Secobarbital</td>
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<td>Isoniazid</td>
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<td>Fluconazole</td>
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<tr>
<td>CYP2C19</td>
<td>Cimetidine</td>
<td>Prednisone</td>
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<td></td>
<td>Indomethacin</td>
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<td></td>
<td>Ketokonazole</td>
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<tr>
<td>CYP2D6</td>
<td>Celecoxib</td>
<td>Imipramine</td>
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<td></td>
<td>Cimetidine</td>
<td>Desipramine</td>
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<td>Cocaine</td>
<td>Amitriptyline</td>
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<td>Methadone</td>
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<td>Pentazocine</td>
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<td>CYP2E1</td>
<td>Disulfiram</td>
<td>Ethanol</td>
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<td>Fluoxetine</td>
<td>Isoniazid</td>
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<tr>
<td>CYP3A</td>
<td>Midazolam</td>
<td>Phenobarbital</td>
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<td></td>
<td>Erythromycin</td>
<td>Dexamethasone</td>
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<td></td>
<td>Methadone</td>
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</tbody>
</table>

**Note:** This is not an exhaustive listing of inducers and inhibitors.

**Conclusion:** Since cimetidine inhibits CYP2D6, less amphetamine will probably need to be given since it will not be able to be metabolized as readily. Most drug interactions are like this: one drug inhibits or competes with the same CYP450 as another drug. The end result is that higher concentrations of one, or both, drugs are present, leading to potential toxicity.
Genotype versus Phenotype

- Genotyping can give us a definitive profile of a given CYP450 enzyme's mutations. But since there are dozens of mutations usually associated with each enzyme, a complete characterization of a CYP450 is not always realistic.
- Without complete sequencing of the entire allele, it may not be possible to entirely rule out a mutation in a patient who shows none of the more common polymorphisms.
- If we consider the number of possible mutations and the possible presence of inducing/inhibiting substances, phenotyping for drug metabolism may sound more reasonable than genotyping.
- Phenotyping involves measuring the metabolism of a probe drug. For example, with CYP2D6, dextromethorphan or debrisoquine can be given to a patient to see how well the drug is metabolized. Both these drugs are safe and extensively metabolized by CYP2D6. This is referred to as 'probe drug testing'. By measuring the parent drug and the metabolite in urine, the metabolic capacity of a CYP450 enzyme can be estimated.
- Such testing is complex and tedious, however, and has not become routine in clinical laboratories. Therefore, genotyping is likely to be the main tool that is used for assessing the PGx of a patient.

TDM and PGx

- Can we use therapeutic drug monitoring (TDM) to assess PGx?
- TDM of the drug in question can also tell us a good deal about a drug's metabolism and will also take into account all the other variables at play (co-medications, diet, impaired organ function, etc.) However, unlike genotyping and probe-drug testing, therapeutic drug monitoring must be performed during therapy, not before. So, in fact, TDM is not really used to predict therapy in PGx but serves as a confirmation of PGx findings.
- TDM and genotyping should be considered complementary and can be used in tandem to, first, predict and then verify appropriate serum drug levels.

The Bottom Line

- In recent years PGx has not expanded and become as widespread as most predicted. The reasons for this are many. One reason is that there are just too many variables at play with drug metabolism (diet, co-medications, age, organ function, etc.) to rely on a simple PGx result. With so many variables the cost of obtaining a PGx genotype on a patient becomes hard to justify. As genetic test prices continues to fall this will present less of a barrier in the future. Another problem has been the lack of clinical studies that show that PGx improves morbidity and mortality for patients. That is, if PGx testing doesn't cause better outcomes, then it is hard for clinicians and patients to justify its cost. There are some studies which suggest, for example, that PGx testing may reduce hospital admissions (for those on warfarin) but to-date there are few large, powerful studies which clearly demonstrate that PGx testing provides added benefit to patients.
- The US Medicare/Medicaid system has also been slow to reimburse for PGx testing. Thus, it has not been adopted by mainly labs or health systems.
- There are some drugs however for which PGx testing is becoming more popular. Some of these drugs have such a high potential for severe, lethal toxicity that PGx testing or enzyme testing for these drugs has become standard of care. Some examples of these drugs and the enzymes that assessed before use include:
  - Irinotecan (where UDP-glucuronosyl transferase 1A1 (UGT1A1) is assessed)
  - 6-mercaptopurine (Thiopurine methyl transferase (TPMT) activity is assessed)
5-Fluorouricil (Dihydropyrimidine dehydrogenase (DPD) activity is assessed)

- Clopidogrel (Plavix) is another drug in which PGx testing is getting more attention. For this anti-platelet drug, CYP2C19 or platelet function is often directly assessed to ensure that the patient is able to convert clopidogrel to its active metabolite to achieve the needed anti-platelet effect.
- By knowing a patient's disposition to specific drugs, the physician should be able to start the patient on an appropriate regimen rather than perfecting treatment based on trial and error. Drugs whose metabolism may prove to be problematic can be avoided, and second-line therapies that are metabolized by different, unaffected enzymes can be chosen.
- Clinical chemists, pharmacologists, and physicians need to translate knowledge of CYP450 polymorphisms into clinically-validated treatment algorithms.
- Dosing recommendations for PM, EM, IM and UM patients are beginning to appear in the literature for various classes of drugs, and the FDA is encouraging the incorporation of pharmacogenomic testing in the development process for new drugs.
IV- Individualized TDM Drug Profiles

Acetylsalicylic acid (Aspirin)

**USUAL DOSAGE**
- Adults (antiinflammatory): 45 to 60 mg/kg/day
- Children (antiinflammatory): 70 to 90 mg/kg/day

**USUAL DOSING INTERVAL**
- Daily dose given in four to six divided doses

**TOXIC EFFECTS**
- Tinnitus, headaches, vertigo, hearing loss
- Gastrointestinal, intolerance
- Bronchospasm.
- Severe chronic and acute Intoxication, central Hyperventilation, respiratory alkalosis, metabolic acidosis (˃400 mg/l; ˃2.9 mmol/l), hyperglycemia (early), Hypoglycemia (late).

**TIME TO PEAK SERUM CONCENTRATION**
- Salicylic acid: 1 to 2 hours (formulation dependent)

**TIME TO ACHIEVE STEADY STATE**
- Salicylic acid: 5 to 7 days of chronic oral dosing

**ELIMINATION HALF-LIFE**
- Acetylsalicylic acid: 15 to 30 min
- The serum half-life and volume of distribution of salicylic acid may increase with increasing dose
- Salicylic acid: 3 hours after single 250 mg dose - 20 hours at higher doses

**ROUTE OF ELIMINATION**
- Acetylsalicylic acid is hydrolyzed to salicylic acid
- Salicylic acid is then metabolized to the following compounds which undergo renal elimination:
  - Salicyluric acid (saturable metabolic pathway)
  - Gentisic acid (first-order pathway)
  - Salicyl acyl glucuronide (first-order pathway)
  - Salicyl phenol glucuronide (saturable metabolic pathway)

**PROTEIN BINDING**
- 50 to 90% (concentration dependent)

**USUAL SAMPLING TIMES**
- 1 to 3 hours after an oral dose (formulation dependent)

**USUAL THERAPEUTIC RANGE**
- Salicylic acid: 150 to 300 mg/l; 1.1 to 2.2 mmol/l (antiinflammatory)

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease:**
- Hypoalbuminemia (decreased protein binding)

**Drugs:**
- Acetylsalicylic acid can cause a conformational change in albumin's structure, resulting in altered protein binding for other drugs
- Corticosteroids decrease steady state levels of salicylates

**Others:**
- Rate of absorption from stomach is pH and formulation dependent (i.e., high pH, slow absorption)
- Systemic acidosis can cause increased tissue uptake reducing the validity of serum level concentrations
- Urinary alkalinization increases renal elimination in overdose

**NOTES:**

1. Half-life is longer in newborns
2. Salicylic acid is excreted unchanged in the urine only 2 to 14 %
3. Therapeutic range is usually lower if the drug is used for analgesia
4. To assess risk of acute toxicity refer to the nomogram of Done (Done AK, Pediatrics (Suppl) 62: 890-897, 1978).
Gentamicin (Cepiophal, Garamycin, Genticin, Gentisone):

**USUAL DOSAGE (IV, IM)**
- **Loading Dose**
  - Adults: 1 to 2 mg/kg
  - Children: 1 to 2 mg/kg
  - Neonates: 2 to 2.5 mg/kg
- **Maintenance Dose**
  - Adults: 3 to 6 mg/kg/day
  - Children: 4 to 10 mg/kg/day
  - Neonates: 2 to 7.5 mg/kg/day

**USUAL DOSING INTERVAL**
- Adults: given in two to four divided doses/day
- Children: given in three to six divided doses/day
- Neonates: given in one to two divided doses/day

**TOXIC EFFECTS**
- Nephrotoxicity.
- Ototoxicity.
- Neuromuscular blockade.

**TIME TO ACHIEVE STEADY STATE**
- Adults: <30 years: 2.5 to 15 hours of chronic dosing / >30 years: 7.5 to 75 hours of chronic dosing
- Children: 2.5 to 12.5 hours of chronic dosing
- Neonates: 10 to 45 hours of chronic dosing

**ELIMINATION HALF-LIFE**
- Adults: < 30 years: 0.5 to 3 hours / >30 years: 1.5 to 15 hours
- Children: 0.5 to 2.5 hours
- Neonates: 2 to 9 hours

**ROUTE OF ELIMINATION**
- Renal excretion 90% unchanged
- No known metabolites

**PROTEIN BINDING**
- ≤ 10%

**USUAL SAMPLING TIMES**
- Peak: 0.5 to 1 hour after the end of 30 minutes infusion (1 hour after IM dose)
- Trough: immediately before next dose

**USUAL THERAPEUTIC RANGE**
- Peak: 5 to 10 mg/l
- Trough: <2 mg/l

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Drugs:**
- Other nephrotoxic drugs which might decrease renal function will cause decreased clearance.
- High concentrations of certain penicillins (e.g., carbenicillin) may inactivate aminoglycosides either in vitro or in vivo especially in patients its severely compromised renal function.

**Others:**
- Renal impairment: ↓ clearance
- Dehydration: ↓ volume of distribution
- Obesity: alters distribution
- Burn patients: ↑ dosage requirement
• Hypermetabolic surgical patients: ↑ clearance 
• Cystic fibrosis: ↑ dosage requirement 

Notes:

1. These are starting dosages which may exceed manufacturers recommendations and reflect the authors' opinions of usual dosages required to achieve therapeutic serum concentrations in patients with serious infections and normal renal function. These dosages require monitoring of serum concentrations.
2. In neonates the dosages should be adjusted based on patient response, serum concentrations, and renal function.
3. Higher dosages may be necessary in select patients.
4. Dosing intervals should be adjusted based on patient response, serum concentrations, and renal function.
5. Once daily dosages have been recommended. At a dosage of 4 mg/kg/day once a day (q.d.) an average peak concentration of 0.2 mg/l was found (Prins et al. 1993, Lancet 341, 335-39). Guidelines for dosage regimens and monitoring may vary.
6. Assuming normal renal function.
7. Peak delayed in patients who have compromised renal function.
8. Usual therapeutic range will be dependent on infection organism, site of infection, immunological status of the patient, and severity of infection. Increases in trough concentrations consistent with tissue accumulation have been associated with toxicity.
NETILMICIN (Netillin, Netromycin)

**USUAL DOSAGE (IV, IM)**

- **Loading Dose**
  - Adults: 1 to 2 mg/kg
  - Children: 1 to 2 mg/kg
  - Neonates: 2 to 2.5 mg/kg
- **Maintenance Dose**
  - Adults: 4 to 8.6 mg/kg/day
  - Children: 4 to 2 mg/kg/day
  - Neonates: 2 to 7.5 mg/kg/day

**USUAL DOSING INTERVAL**

- Adults: given in two to four divided doses/day
- Children: given in three to six divided doses/day
- Neonates: given in one to two divided doses/day

**TOXIC EFFECTS**

- Nephrotoxicity
- Ototoxicity
- Neuromuscular blockade

**TIME TO ACHIEVE STEADY STATE**

- Adults: <30 years- 2.5 to 15 hours of chronic dosing / >30 years- 7.5 to 75 hours of chronic dosing
- Children: 2.5 to 12.5 hours of chronic dosing
- Neonates: 10 to 45 hours of chronic dosing

**ELIMINATION HALF-LIFE**

- Adults: < 30 years- 0.5 to 3 hours / >30 years- 1.5 to 15 hours
- Children: 0.5 to 2.5 hours
- Neonates: 2 to 9 hours

**ROUTE OF ELIMINATION**

- Renal excretion 90% unchanged
- No known metabolites

**PROTEIN BINDING**

- ≤ 10%

**USUAL SAMPLING TIMES**

- Peak: 0.5 to 1 hours after the end of 30 minutes infusion {1 hour after IM dose}
- Trough: immediately before next dose

**USUAL THERAPEUTIC RANGE**

- Peak: 5 to 12 mg/l {11 to 25 umol/l}
- Trough: <3 mg/l {6umol/l}

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Drugs:**

- Other nephrotoxic drugs which might decrease renal function will cause decreased clearance.
- High concentrations of certain penicillins (e.g., carbenicillin) may inactivate aminoglycosides either in vitro or in vivo especially in patients with severely compromised renal function.

**Others:**

- Renal impairment: ↓ clearance
- Dehydration: ↓ volume of distribution
- Obesity: alters distribution
- Burn patients: ↑ dosage requirement
Hypermetabolic surgical patients: ↑clearance
Cystic fibrosis: ↑ dosage requirement

Notes:
1. These are starting dosages which may exceed manufacturers recommendations and reflect the authors opinions of usual dosages required to achieve therapeutic serum concentrations in patients with serious infections and normal renal function. These dosages require monitoring of serum concentrations.
2. In neonates the dosages should be adjusted based on patient response, serum concentrations, and renal function.
3. Higher dosages may be necessary in select patients.
4. Dosing intervals should be adjusted based on patient response, serum concentrations, and renal function.
5. Once daily dosages have been recommended. At a dosage of 6.6 mg/kg/day once a day (q.d.) an average peak concentration of 21.3 mg/l was found (see ref. 20 page 16). Guidelines for dosage regimens and monitoring may vary.
6. Assuming normal renal function.
7. Peak delayed in patients who have compromised renal function.
8. Usual therapeutic range will be dependent on infection organism, site of infection, immunological status of the patient, and severity of infection. Increases in trough concentrations consistent with tissue accumulation have been associated with toxicity.
### VANCOMYCIN : (Fibrantil, Vancocin)

#### USUAL DOSAGE (IV)
- Adults: 20 to 40 mg/kg/day
- Children: 40 to 60 mg/kg/day
- Neonates: 30 mg/kg/day

#### USUAL DOSE INTERVAL
- Adults: given in two to four divided doses/day
- Children: given in two to four divided doses/day
- Neonates: given in two divided doses/day

#### TOXIC EFFECTS
- Hypersensitivity: skin rashes and anaphylaxis/
  "Red-neck” syndrome/
- Chills and fever/
- "Red-neck" syndrome/
- Phlebitis and pain at site of injection
- Ototoxicity
- Nephrotoxicity (rare)

#### TIME TO ACHIEVE STEADY STATE
- ~20 to 30 hours of chronic dosing

#### ELIMINATION HALF-LIFE
- Adults: 4 to 10 hours
- Children: 2 to 3 hours
- Neonates: 6 to 10 hours

#### ROUTE OF ELIMINATION
- Renal >90 % unchanged in urine

#### PROTEIN BINDING
- 30 to 55 %

#### USUAL SAMPLING TIMES
- Peak: 1 hour after the end of intravenous infusion
- Trough: immediately prior to next dose

#### USUAL THERAPEUTIC RANGE
- Peak: 20 to 40 mg/l (14 to 28 umol/l)
- Trough: 5 to 10 mg/l (3 to 7 umol/l)

#### SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS
- Renal disease may increase serum concentration

#### Notes:
- Peak delayed in patients who have compromised renal function
CARBAMAZEPINE (Tegretol):

**USUAL DOSAGE (IV)**
- Adults: 5 to 25 mg/kg/day orally {anticonvulsant}/ 3 to 20 mg/kg/day orally {treatment of trigeminal neuralgia}
- Children: 5 to 20 mg/kg/day orally {anticonvulsant}

**USUAL DOSING INTERVAL**
- given in two to four divided doses depending on patient tolerance

**TOXIC EFFECTS**
- Diplopia, blurred vision, nystagmus
- Headache, dizziness, ataxia, sedation
- Nausea, vomiting
- Hyponatremia, water intoxication
- Exacerbation of seizure frequency
- Disturbances of heart rhythm and conduction
- Hypersensitivity reaction

**Time to peak serum concentration**
- Quite variable. Usually 4 to 6 hours after dosing with conventional formulations. Usually more than 12 hours after a single dose with sustained release formulations, in overdosing after 24 hours

**TIME TO ACHIEVE STEADY STATE**
- After 2 to 6 days of chronic oral dosing

**ELIMINATION HALF-LIFE**
- 6 to 12 hours {chronic dosing}

**ROUTE OF ELIMINATION**
- ~99% by hepatic metabolism
- ~1% excreted unchanged in urine
- The active 10,11-epoxide metabolite may contribute to therapeutic and toxic effects

**PROTEIN BINDING**
- 65 to 80%

**USUAL SAMPLING TIMES**
- Chronic oral dosing: trough immediately before next dose

**USUAL THERAPEUTIC RANGE**
- 4 to 11 mg/l {17 to 47 umol/l}

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Hepatic: ↓ clearance

**Other**
- Children: ↑ clearance / - Old age: ↓ clearance
- Pregnancy: ↑ clearance

**Drug interactions:**
- Cimetidine, danazol, diltiazem, ↓ clearance
- Fluoxetine, fluvoxamine, ↓ clearance
- Isoniazid, macrolide antibiotics, ↓ clearance
- Propoxyphene, verapamil, ↓ clearance
- Valproic acid, Valpromide: ↑ level of 10,11-epoxide metabolite
- Activated charcoal (used in cases of toxicity or overdose): ↑ clearance by ↓ absorption
- Barbiturates, felbamate, phenytoin: ↑ clearance

Dr: Ahmed Refat & Dr: Maha Al-Mazroua
Notes:

1. Patients receiving concurrent treatment with barbiturates or phenytoin generally require larger dosages compared to patients on monotherapy. Treatment should be initiated with a low dose, usually one-third to one-fourth of the maintenance dose, and increased gradually by about 25% on a weekly basis so that full doses are achieved in approximately 3 to 4 weeks. Abrupt discontinuation of treatment may result in status epilepticus.

2. Sustained release formulations may allow prolongation of dosing interval.

3. Skin rashes are common (about 10%). Rare hypersensitivity or idiosyncratic reactions may include fever, lymphadenopathy, blood dyscrasias, hepatotoxicity, pneumonitis. Taken during pregnancy, carbamazepine may increase the rate of congenital malformations.

4. At initiation of treatment. Serum drug levels may decrease after 1 to 3 weeks due to autoinduction, necessitating follow-up levels to verify stabilization of serum concentration.

5. Half-lives are much longer (15 to 50 hours) after a single dose in non-induced state. Half-lives are shorter in children than in adults.

6. Serum drug levels may fluctuate markedly. An additional sample at time of peak may provide useful information in some patients.

7. Lower concentrations are usually adequate for trigeminal neuralgia or other neuropathic syndromes.

8. Carbamazepine is an enzyme inducer and may stimulate the metabolism of concurrently administered drugs such as valproic acid, cyclosporin, glucocorticoids, oral anticoagulants and steroid oral contraceptives. The likelihood that enzyme induction will gradually decrease following carbamazepine discontinuation may necessitate eventual dosage reduction of these concurrent drugs.
PHENOBARBITAL (Phenobarbitone):

**USUAL DOSAGE**
- Adults: 1 to 4 mg/kg/day orally
- Children: 2 to 5 mg/kg/day orally

**USUAL DOSING INTERVAL**
- May be given as once daily dose at bedtime

**TOXIC EFFECTS**
- Sedation, tiredness, fatigue, confusion
- Cognitive impairment, depression
- Irritability, hyperactivity (in children)
- Vitamin D deficiency
- Ataxia, dysarthria
- Exacerbation of seizure frequency
- Decreased libido, impotence
- Dupuytren's contraction, shoulder stiffness
- Hypersensitivity reactions

**Time to peak serum concentration**
- Variable usually 1 to 3 hours after dosing

**TIME TO ACHIEVE STEADY STATE**
- Adults and adolescents: 10 to 25 days of chronic oral dosing
- Infants and children: 8 to 20 days of chronic oral dosing

**ELIMINATION HALF-LIFE**
- Adults: ~100 hours (range 50 to 150)
- Infants and children: ~65 hours (range 40 to 130)
- Newborns: 60 to 200 hours

**ROUTE OF ELIMINATION**
- ~70% by hepatic metabolism
- 20 to 40% excreted unchanged in urine
- No active metabolites

**PROTEIN BINDING**
- ~50%

**USUAL SAMPLING TIMES**
- Due to the long half life, fluctuations in serum drug concentration at steady state are usually negligible. However, when making comparative measurements, it is advisable that the sampling time be consistent.

**USUAL THERAPEUTIC RANGE**
- 10 to 40 mg/l (43 to 172 umol/l)

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Hepatic impairment will decrease metabolism
- Moderate to severe renal impairment will decrease clearance of unchanged drug

**Other**
- Neonates: ↓ clearance
- Children: ↑ clearance
- Pregnancy: ↑ clearance
- Urine alkalization: ↑ clearance
Drug interactions:

- chloramphenicol, dextropropoxyphene,
- dicoumarol, furosemide, methsuximide,
- methylphenidate, phenytoin,
- sulthiame, valproic acid

\[ \text{\textsuperscript{\(\downarrow\text{clearance}\)}} \]

- Activated charcoal: \(\uparrow\) clearance by \(\downarrow\) absorption

Notes:

1. Phenobarbital may also be used intravenously for the treatment of status epilepticus. A possible dosing scheme involves a loading dose at a rate not exceeding 100 mg/min until seizures stop or a total dose of 10 mg/kg is administered. If seizures continue, infusion can be continued at a rate of 50 mg/min until a total dose of 20 mg/kg is reached. Sedation and respiratory depression occur frequently with intravenous doses and adequate support facilities should be readily available.

2. Hypersensitivity reactions are relatively rare and may include rashes, fever and eosinophilia. Taken during pregnancy, Phenobarbital may increase the rate of congenital malformations.

3. Longer half-lives are observed in premature newborns.

4. Some patients may be controlled at lower concentrations. Since tolerance develops to the sedative effects of phenobarbital, chronically treated patients may tolerate, without major adverse effects, serum drug concentrations which would be very toxic upon acute exposure. To minimize initial adverse effects, treatment should be started at a low dosage whenever possible and titrated upwards. Abrupt discontinuation of treatment may result in status epilepticus.

5. Phenobarbital is present in serum of patients treated with primidone, methylphenobarbital (mephobarbital) and eterobarbital.

6. Phenobarbital is an enzyme inducer and may stimulate the metabolism of concurrently administered drugs such as valproic acid, carbamazepine, cyclosporine, glucocorticoids, oral anticoagulants, and steroid oral contraceptives. The likelihood that enzyme induction will gradually decrease following Phenobarbital discontinuation may necessitate eventual dosage reduction of these concurrent drugs.
PHENYTOIN (Dilantin, Epanutin)

USUAL DOSAGE
- Adults: 3 to 6 mg/kg/day orally
- Children: 5 to 9 mg/kg/day orally

USUAL DOSING INTERVALS
- Adults: 1 or 2 daily doses
- Children: 2 to 3 divided oral doses

TOXIC EFFECTS
- Nystagmus, dysarthria, diplopia, ataxia
- Cognitive dysfunction, behavioural problems
- Exacerbation of seizure frequency
- Encephalopathy
- Folate and vitamin D deficiency
- Coarse features, hirsutism, acne, gum hypertrophy. Hypersensitivity reactions

Time to peak serum concentration
- Usually 2 to 6 hours after oral dosing
- With sustained release formulations, peak may occur 3 to 9 hours (or even later) after dosing

TIME TO ACHIEVE STEADY STATE
- Phenytoin exhibits dose-dependent kinetics and the time to reach steady state increases with increasing serum concentrations, usually steady state is achieved after 4 to 24 days of chronic oral dosing

ELIMINATION CHARACTERISTICS
- The term half life is not a useful parameter with drugs that exhibit dose-dependent pharmacokinetics. More useful terms would be maximal rate of metabolism ($V_{\text{max}}$) and concentration at which rate of metabolism is half of its maximal rate ($K_m$):
  - $V_{\text{max}}$ 100 to 1000 mg/day
  - $K_m$ 1 ro 15 mg/l (4 ro 59 umol/l)

ROUTE OF ELIMINATION
- More than 95% by hepatic metabolism
- Less than 5% excreted unchanged in urine
- No active metabolites

PROTEIN BINDING
- ~92%

USUAL SAMPLING TIMES
- Due to slow oral absorption and elimination, fluctuation in serum drug concentration at steady state are usually relatively small; however, when making comparative measurements, it is advisable that sampling time be consistent (ideally: trough level)

USUAL THERAPEUTIC RANGE
- Adults, children, infants > 3 months: 10 to 20 mg/l (40 to 80 umol/l)
- Preterm, term neonates and Infants 2 weeks to 3 months: 6 to 14 mg/l (24 to 55 umol/l)

SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS

Disease
- Mononucleosis: ↑ clearance
- Chronic liver disease: ↓ clearance
- Renal disease: see note 4

Other
- Neonates: ↓ Clearance
- Children: ↑ clearance
- Pregnancy: ↑ clearance
- Urine alkalinization: ↑ clearance

**Drug interactions:**

- Some antacids, antineoplastics, nasogastric feeding formulas, activated charcoal, and sucralfate may reduce phenytoin absorption
- Some drugs may displace phenytoin from protein binding sites in serum, usually this results in a decrease in total serum phenytoin concentration without change in free concentration. Relationship between total serum concentration and response will be altered.
- Phenytoin may also be used intravenously for the treatment of status epilepticus. A possible dosing scheme involves a loading dose of 18 mg/kg at a rate not exceeding 50 mg/min. Hypotension and a systole may occur and adequate support facilities should be readily available. Diazepam or lorazepam are usually combined with phenytoin in the treatment of status epilepticus. Intravenous maintenance doses of phenytoin should be given in two to three divided daily doses
- Phenobarbital may cause a transient increase due to competitive inhibition of metabolism or a decrease due to enzyme induction

**Notes:**

1. Phenytoin is usually started at a low dosage and increased gradually according to clinical response. If rapid response is required, loading doses may be given. Dosage adjustment should be cautious due to the non-linear relationship between sodium salt and free acid (10% dosage difference), may cause disproportionately large increase in serum drug concentration. Abrupt withdrawal of treatment may result in status epilepticus. Phenytoin may also be used intravenously for the treatment of status epilepticus.
   - Possible dosing scheme involves a loading dose of 18 mg/kg at a rate not exceeding 50 mg/min. Hypotension and a systole may occur and adequate support facilities should be readily available. Diazepam or lorazepam are usually combined with phenytoin in the treatment of status epilepticus. Intravenous maintenance doses of phenytoin should be given in two to three divided daily doses
2. Hypersensitivity reactions are relatively rare and may include: Skin rashes, fever, and eosinophilia. Lymphadenopathy, systemic lupus erythematosus, hepatotoxicity, blood dyscrasias. Taken during pregnancy, phenytoin may increase the rate of congenital malformations.
3. For practical purposes, however, it can be estimated that half lives range from 20 to 100 hours in most cases, the longest values being recorded at high serum concentrations. In infants and children, half-lives range from 10 to 30 hours at concentration between 10 and 20 mg/l (shorter or higher values are recorded at concentrations below or above this range respectively)
4. Binding to serum proteins may decrease in conditions associated with hypoalbuminemia (malnutrition, nephritic syndrome, neonates, elderly patients, pregnancy, etc.) or accumulation of endogenous displacing agents (hyperbilirubinemia, uremia). Other drugs such as sulfonamides, phenylbutazone, salicylates, sulfonylureas and most notably, valproic acid, may also displace phenytoin from serum proteins and increase its free fraction. Since only the unbound (free) drug is pharmacologically active, in the presence of decreased binding the total serum phenytoin concentration may underestimate the amount of drug which is active, and therapeutic and toxic effects will appear at lower total concentration. In these situations, it may be useful to measure the free concentration. A therapeutic range of 1 to 2 mg/l (4 to 8 umol/l) is suggested for free phenytoin
5. Some patients may be controlled at lower concentrations. See also note 4
6. Phenytoin is an enzyme inducer and may stimulate the metabolism of concurrently administered drugs such as valproic acid, carbamazepines, cyclosporine, glucocorticoids, oral anticoagulants and steroid oral contraceptives
VALPROIC ACID (Convulex, Depakene, Epilim, Orfirl)

**USUAL DOSAGE**
- Adults: 10 to 45 mg/kg/day orally
- Children: 10 to 60 mg/kg/day orally

**USUAL DOSING INTERVAL**
- Given in one to four divided doses

**TOXIC EFFECTS**
- Gastric irritation, nausea and vomiting
- Weight gain
- Sedation, stupor, tremor
- Thrombocytopenia
- Hepatotoxicity, pancreatitis
- Teratogenicity (neural tube defects)
- Hyperammonemia

**Time to peak serum concentration**
- Syrup: 0.5 to 1 hour after dosing
- Capsules or plain tablets: 0.5 to 2 hours after dosing
- Enteric coated tablets: 3 to 8 hours after dosing

**TIME TO ACHIEVE STEADY STATE**
- After 2 to 4 days of chronic oral dosing

**ELIMINATION HALF-LIFE**
- Adults: 6 to 17 hours
- Infants and children: 5 to 15 hours
- Newborns (≤ 2 months): 15 to 60 hours

**ROUTE OF ELIMINATION**
- About 95% by hepatic metabolism
- Less than 5% excreted unchanged in urine
- Reactive metabolites may contribute to hepatotoxicity and possibly teratogenicity

**PROTEIN BINDING**
- ~90%

**USUAL SAMPLING TIMES**
- Chronic oral dosing: trough immediately before next dose

**USUAL THERAPEUTIC RANGE**
- 50 to 100 mg/l (347 to 693 umol/l)

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Hepatic disease: see note 4
- Renal disease: see note 4
- Hypoalbuminemia: see note 4

**Other**
- Neonates: ↓ clearance
- Children: ↑ clearance
- Pregnancy: ↑ clearance
- Old age: see note 4

**Drug interactions:**
- Activated charcoal, some antacids and Some antineoplastics: ↓ absorption
- Salicylates: see note 4 & 9
Barbiturates, Phenytoin, Carbamazepine: ↑clearance

Some drugs displace valproic acid from serum protein binding sites: see note4

Notes:

1. Available in several dosage forms, e.g., valproic acid, sodium valproate, magnesium valproate. Treatment is usually initiated with a relatively low dose and increased gradually. Abrupt discontinuation of treatment may result in status epilepticus.
2. Sustained release formulations may allow prolongation of dosing interval.
3. Absorption from enteric coated tablets may be markedly delayed by food.
4. Protein binding decreases at high serum concentrations. Binding may decrease in conditions associated with hypoalbuminemia (malnutrition, nephrotic syndrome, neonates, elderly patients, Pregnancy, etc.). Accumulation of endogenous displacing agents (uremia), and concurrent treatment with displacing drugs, such as salicylates and phenylbutazone. Since only the unbound (free) drug is pharmacologically active, in the presence of decreased binding the total serum valproic acid concentration may underestimate the amount of drug high is active, and therapeutic and toxic effects will appear at lower total concentration.
5. Serum drug levels may fluctuate markedly. An additional sample at time of peak may provide useful information in some patients.
6. Valproic acid is the active moiety in the serum of patients treated with divalproex sodium (depakote) and valpromide (depamide).
7. Some patients with seizures that are difficult to control may benefit from concentration greater than 100 mg/L without adverse effects.
8. Valproic acid may inhibit the metabolic elimination of Phenobarbital, phenytoin, carbamazepine-10,11-epoxide, and lamotrigine. Valproic acid displaces phenytoin from serum protein binding sites. A favourable (synergistic) pharmacodynamic interaction between ethosuximide and valproic acid may occur in patients with certain types of absence seizures. Valproic acid may increase serum ethosuximide concentrations.
9. Salicylates may inhibit the metabolism of valproic acid in addition to displacing it from protein binding sites. These two mechanisms have opposing effects on total clearance of valproic acid.
METHOTREXATE (Methotrexate LPD, Mexate):

**USUAL DOSAGE**
- The dosage for methotrexate is widely varied, ranging from low dose oral therapy (≈ 20 mg/m²) to high dose IV therapy (1-12 g/m²) with leucovorin rescue. Thus, the dosage of Methotrexate must follow a specific treatment protocol.

**USUAL DOSING INTERVAL**
- Consult specific treatment protocol (see above)

**TOXIC EFFECTS**
- Nausea and vomiting
- Myelosuppression
- Mucositis
- Renal dysfunction
- Hepatic dysfunction
- Leukoencephalopathy
- Rash

**TIME TO ACHIEVE STEADY STATE**
- Approximately 12 to 24 hours of chronic dosing

**ELIMINATION HALF-LIFE**
- 2 to 4 hours, initial half-life
- 8 to 15 hours, terminal half-life

**ROUTE OF ELIMINATION**
- Renal excretion 70-90% unchanged
- Renal excretion of methotrexate and 7-hydroxymethotrexate.
- Metabolism up to ~ 30%; major extracellular metabolite 7-hydroxy methotrexate (little cytotoxic activity; poor solubility in acidic urine)

**PROTEIN BINDING**
- 50 to 60%

**USUAL SAMPLING TIMES**
- The sampling times for methotrexate will depend on dose, duration of infusion and clinical status of the patient (consult specific treatment protocol). These are generally used to guide adjustment of leucovorin rescue doses

**USUAL TOXIC RANGE**
- A usual therapeutic range for methotrexate has not been defined. The minimum cytotoxic concentration is ≈ 0.01 µmol/l.
- Serum concentrations which have been associated with increased risk of toxicity after a six-hour high-dose (~ 5 g/m²) infusion, when only low-dose leucovorin rescue is given:
  
  - 24 hours ≥5 µmol/l give higher dose of leucovorin or extend rescue
  - 48 hours ≥0.5 µmol/l beyond planned endpoint
  - 72 hours ≥0.05 µmol/l

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Renal disease↓ clearance
- Aciduria (urine PH<6.5)
- Decreased urine flow
- Ascites, pleural effusion, 3rd space fluid collection
- GI obstruction
- Rash

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• Drugs:
  - Nonabsorbable antibiotics
  - Concurrent or previous therapy with neoplastic drugs
  - Probenecid, salicylates
  - NSAIDs, sulfonamides

\[ \text{↓ absorption} \]

\[ \text{↓ clearance} \]

Notes:

1. “toxicity” assignment is dependent on duration of exposure, as well as serum concentration, and is probably influenced by intensity of cumulative exposure prior to measured points and beyond measured points. For leucovorin dosage guidelines based on methotrexate serum concentration see next table.

<table>
<thead>
<tr>
<th>Methotrexate Serum concentration more than 24 hrs from beginning of infusion</th>
<th>Leucovorin Approximate dose required</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 50 µmol/l</td>
<td>500 mg/m² IV Q 6 hours</td>
</tr>
<tr>
<td>10 to 20 µmol/l</td>
<td>200 mg/m² IV Q 6 hours</td>
</tr>
<tr>
<td>5 to 10 µmol/l</td>
<td>100 mg/m² IV Q 6 hours</td>
</tr>
<tr>
<td>1 to 5 µmol/l</td>
<td>30 mg/m² IV or PO Q 6 hours</td>
</tr>
<tr>
<td>0.5 to 1 µmol/l</td>
<td>15 mg/m² PO Q 6 hours</td>
</tr>
<tr>
<td>0.1 to 0.5 pmol/l</td>
<td>15 mg/m² PO Q 12 hours</td>
</tr>
<tr>
<td>0.01 to 0.1 µmol/l</td>
<td>5 to 10 mg/m² PO Q 12 hours</td>
</tr>
</tbody>
</table>

2. Methotrexate (MTX) concentrations should be monitored and leucovorin administration should be continued in “high risk” patients until serum MTX concentrations are < 0.05 µmol/l. Leucovorin dosages may be reduced, as indicated, as MTX serum concentrations decrease.
THEOPHYLLINE (Aminophylline, Theo-dur, theo 24):

**USUAL DOSAGE**

<table>
<thead>
<tr>
<th>Loading dosage</th>
<th>Theophylline dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No prior theophylline administration in previous 24 hours</td>
<td>5 mg/kg IV over 30 min</td>
</tr>
<tr>
<td>• Prior theophylline administration, Obtain serum concentration;</td>
<td>2 mg/kg IV over 30 min</td>
</tr>
<tr>
<td>in an Emergency without symptoms of intoxication.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance dosage</th>
<th>Theophylline Infusion Rate (mg/kg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults (healthy nonsmokers)</td>
<td>0.4</td>
</tr>
<tr>
<td>• Adults (smokers)</td>
<td>0.6</td>
</tr>
<tr>
<td>• Adults (cardiac decompensation and/or liver dysfunction)</td>
<td>0.2</td>
</tr>
<tr>
<td>• Children (&gt;9 years; healthy)</td>
<td>0.7</td>
</tr>
<tr>
<td>• Children (1 to 9 years)</td>
<td>0.8</td>
</tr>
<tr>
<td>• Infants (4 to 52 weeks)</td>
<td>0.008 (age in weeks + 0.021)</td>
</tr>
<tr>
<td>• Neonates</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic dosage</th>
<th>Theophylline dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults (healthy nonsmokers)</td>
<td>10-15</td>
</tr>
<tr>
<td>• Adults (smokers)</td>
<td>15-18</td>
</tr>
<tr>
<td>• Adults (cardiac decompensation and/or liver dysfunction)</td>
<td>4-8</td>
</tr>
<tr>
<td>• Adolescents (12 to 16 years)</td>
<td>18</td>
</tr>
<tr>
<td>• Children (9 to 12 years)</td>
<td>20</td>
</tr>
<tr>
<td>• Children (1 to 9 years)</td>
<td>24</td>
</tr>
<tr>
<td>• Infants (6 to 51 weeks)</td>
<td>0.3 (age in weeks + 8)</td>
</tr>
<tr>
<td>• Neonates (premature or normal)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**USUAL DOSING INTERVAL**

- **Intravenous**
  - Loading doses of theophylline should be infused over 30 min.
  - Maintenance doses of theophylline should be calculated for a 24 hour period and then administered as a continuous intravenous infusion starting 30 to 60 min after loading dose.

- **Oral therapy**
  - Dosing intervals will vary dependent upon product formulation, age of patient, and patients elimination rate. In case of chronic dosage sustained release formulations are commonly used.
  - However, the following will provide guidelines for dosage intervals.

<table>
<thead>
<tr>
<th>Total daily dosage</th>
<th>Given in divided Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Release</td>
<td>3 to 4</td>
</tr>
<tr>
<td>Sustained Release:</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Adults</td>
<td>1 to 2</td>
</tr>
</tbody>
</table>

**TOXIC EFFECTS**

- Nausea, vomiting, diarrhea, insomnia, headache
- Irritability, nervousness
- Seizures, sinus tachycardia, cardiac arrhythmias, cerebral hypoxia, cardiorespiratory collapse

**Time to peak serum concentration**
- This is dependent upon product formulation, since sustained release products have a very prolonged time to “peak”, compared to conventional products (about 3 to 8 hours longer)

**TIME TO ACHIEVE STEADY STATE**
- Adults: ~2 to 3 days of chronic oral dosing
- Children: ~1 to 2 days of chronic oral dosing
- Infants: ~1 to 5 days of chronic oral dosing
- Newborn: ~120 hours of chronic oral dosing
- Premature neonates: ~150 hours of chronic oral dosing

**RATE OF ELIMINATION**
- Adults (healthy, nonsmokers): 9 hours (range 3 to 12)
- Adults (healthy, smokers): 4 hours
- Adults (liver cirrhosis): 10 to 56 hours
- Children: 4 hours (range 2 to 10)
- Infants (4 to 52 weeks): 3 to 14 hours
- Neonates:
  - Premature: 30 hours
  - Normal newborn: 24 hours

**RATE OF ELIMINATION**
- Hepatic metabolism the renal excretion of relatively inactive metabolites, caffeine is a metabolite in newborn
- Renal excretion of less than 10% unchanged drug (greater in newborn)

**PROTEIN BINDING**
- 55 to 66% (healthy adults)
- ~36% (neonates, adults with liver cirrhosis)

**USUAL SAMPLING TIMES**
- **Intravenous**
  - Prior to intravenous infusion.
  - 30 min after completion of loading dose to measure adequacy of dose.
  - 4 to 6 hours after beginning continuous infusion therapy (presteady state but used to establish trend) or before next infusion.
- **Oral, Peak**
  - 2 hours after administration of a product with rapid release properties.
  - 4 to 8 hours after administration of a product with sustained release properties.
- **Oral, Trough**
  - Immediately before next oral dose.

**USUAL THERAPEUTIC RANGE**
- Asthma (bronchodilator) 8 to 20 mg/l: (44 to 111 µmol/l)
- Neonatal apnea 6 to 11 mg/l: (33 to 61 µmol/l)

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**
- **Disease**
  - Fever associated with upper respiratory illness
  - Cor pulmonale
  - Acute pulmonary edema
  - Hepatic cirrhosis
  - Cardiac decompensation
• **Drugs:**
  - Erythromycin
  - Cimetidine
  - Ciprofloxacin
  - Enoxacin
  - Verapamil
  - Allopurinol
  - Aminoglutethimide
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampicin

• **Other**
  - Smoking: ↑clearance
  - Age (Neonates): ↓clearance
  - Age (> 60 years): ↓clearance

**Notes:**

1. Aminophylline contains ~ 80% theophylline.
2. At a relative constant Vd of 0.5 l/kg lean body weight or moderate obesity the following relation is valid: 1 mg/kg -2 mg/l
3. Maintenance dosage should be altered based on serum concentration data determined at the end of this loading dose. If additional loading dose is required, administer necessary dose and redraw serum sample. Further dosage adjustment (maintenance or chronic dosages) should be made with serum concentration results as a guide. Clearance of theophylline in an adult, healthy nonsmoker is 0.04 l/kg/hour. To achieve a concentration of 10 mg/l, dosage of 0.4 mg/kg/hour is reasonable.
4. This dosage of theophylline is intended only as a guide. Increases or decreases in the dosage should be made based upon theophylline serum concentration data. A dosage not tolerated by any patient should be immediately discontinued.
5. Within the therapeutic range the probability of toxic effects is < 5%. Values > 20 mg/l have higher probability and values > 35 mg/l have high probability of toxic effects.
6. This time is decreased in smokers and increased in patients with cardiac decompensation of hepatic failure. It may be increased in children near upper end of therapeutic range (e.g., > 15 mg/l) if saturation of metabolism occurs.
7. Morning trough levels may be greater than evening levels.
DOGXIN (Lanoxin):

**USUAL DOSAGE**

- **Loading dosage (rapid digitalizing)**
  
  **Oral**
  - Adults and children > 10 years: 12 to 20 µg/kg
  - Children (2 to 10 years): 10 to 40 µg/kg
  - Infants (1 to 24 months): 20 to 40 µg/kg
  - Neonates (0 to 4 weeks): 20 to 30 µg/kg
  - Administer in 3 to 4 divided doses over 24 hours

- **Intravenous**
  - Use approximately 0.8 x the oral loading dose. Administer in 3 to 4 divided doses over 5 to 30 minutes (at least 4 hour intervals). Omit doses if these are signs of digoxin toxicity after the first or second dose; use the actual amount administered to calculate the maintenance dose

- **Maintenance dosage**
  - Adults
    - Normal renal function: 125 to 500 µg/day PO
    - Renal failure: see note 2 and table below
  - Children (2 to 10 years): 8 to 10 µg/kg/day PO
  - Infants (1 to 24 months): 14 to 18 µg/kg/day PO
  - Neonates (0 to 4 weeks): 8 to 10 µg/kg/day PO
  - Adjust on the basis of the final loading dose and estimated renal function and, in atrial fibrillation, on the basis of heart rate. Suggested maintenance doses, based on creatinine clearance, are shown in the table below:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Fraction of loading dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.33</td>
</tr>
<tr>
<td>50</td>
<td>0.25</td>
</tr>
<tr>
<td>25</td>
<td>0.20</td>
</tr>
<tr>
<td>10</td>
<td>0.16</td>
</tr>
<tr>
<td>0</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**USUAL DOSING INTERVAL**

- Once daily for adult patients receiving < 0.25 mg/day and twice daily for patients receiving > 0.25 mg/day. Divide the dose
- If there are gastrointestinal side effects, such as nausea, anorexia or diarrhea.
- Divide the dose into 2 or 3 daily doses for paediatric patients

**TOXIC EFFECTS**

- Cardiovascular:
  - Ventricular dysrhythmias, including multifocal PVC, ventricular tachycardia.
  - AV block, accelerated A-V junctional rhythms.
  - Sinus bradycardia or complete SA block.
  - Atrial fibrillation with slow ventricular rate.
- Gastrointestinal:
  - Anorexia, nausea, vomiting, diarrhea.
- Neurological:
  - Headache, fatigue, malaise, disturbance of color vision

**Time to peak serum concentration**

- Intravenous:

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Peak concentration is usually reached immediately after administration. However, this does not accurately reflect tissue digoxin concentration and thus pharmacological effect (see usual sampling times).

- **Oral:**
  Peak concentration following oral therapy is usually reached in 60 to 90 minutes after administration (see also above, intravenous).

**TIME TO ACHIEVE STEADY STATE**
- Normal renal function: ~ 5 to 7 days of chronic dosing
- Reduced renal function: ~ Greater than 7 days, depending upon degree of reduction

**ELIMINATION HALF-LIFE**
- Adults mean 40 hours, range 20 to 50 hours
- Premature neonates 56 to 88 hours
- Full term neonates 35 to 42 hours
- Infants 18 to 33 hours
- Children ~ 12 to 24 hours

**ROUTE OF ELIMINATION**
- Renal 75 to 80% excreted unchanged
- Hepatic ~ 30% (may be increased substantially in patients with renal impairment)

**PROTEIN BINDING**
- ~20%

**USUAL SAMPLING TIMES**
- 8 to 24 hours after dose administered (better correlation of serum and tissue concentrations)

**USUAL THERAPEUTIC RANGE**
- 0.8 to 2.0 µg/l (1.0 to 2.6 nmol/l)

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Renal disease
- Severe, uncompensated heart failure

**Drugs:**
- Spironolactone
- Liquid antacids and kaolin-pectin preparations ↓ absorption
- Quinidine, amiodarone: ↑ serum concentration

**Notes:**
1. The preferred method of administering the loading dose is orally, and the majority of patients receive their loading dose by this route. Intravenous loading is generally reserved for patients with life-threatening tachyarrhythmias responsive to the drug. The dose varies, depending upon the age of the patient and renal function. For patients with severe renal impairment who chose a loading dose at the low end of the range to compensate for a reduction in the volume of distribution. In most clinical situations rapid digitalizing is not necessary and treatment is started with the maintenance dose.
2. In adults with renal failure, maintenance dose regimen should be adjusted to individual patient requirements.
3. The dosing intervals listed are only guidelines. Each patient should have a dosing interval selected individually based on age, clinical response, and renal function.
4. For serum concentrations to best reflect cardiac activity, serum samples should be taken when digoxin is in equilibrium between serum and tissue. The time to equilibrium following either oral or IV digoxin is usually 8 to 12 hours.
5. Depends on renal function e.g., up to 120 hours in renal failure.
6. There are other factors which do not affect digoxin serum concentrations, but do affect the pharmacological effect of digoxin, for example hypokalemia, hypomagnesemia, hypercalcemia, and acid-base balance. These may act by affecting myocardial sensitivity to digoxin or by affecting the oral absorption of digoxin tablets. The user is referred to pharmacology texts for full lists of these factors.
7. Acetyldigoxin is rapidly and totally converted to digoxin. Methyldigoxin is converted to about 50% of an equivalent dose of digoxin.
8. Bioavailability of digoxin products is highly variable (70 to 100%) depending on the formulation.
CYCLOSPORIN A (Sandimmun):

**USUAL DOSAGE**
- Starting doses: (Monotherapy) 10 to 15 mg/kg/day - (Combination therapy) 7 to 10 mg/kg/day
- Chronic maintenance doses: ~2 to 6 mg/kg/day
- Autoimmune disease: 2.5 to 5 mg/kg/day

**USUAL DOSING INTERVAL**
- Adults: once or twice daily
- Children: may require three times daily dosing

**TOXIC EFFECTS**
- Renal dysfunction/raised serum creatinine
- Hepatic impairment, hypertension, hypomagnesaemia
- Hypertrichosis, gum hyperplasia

**Time to peak serum concentration**
- ~3 hours after oral administration

**TIME TO ACHIEVE STEADY STATE**
- 3 to 5 days of chronic dosing

**ELIMINATION HALF-LIFE**
- Adults: 15 hours (range 4 to 50).
- Children: 9 hours (range 3 to 20)

**ROUTE OF ELIMINATION**
- Hepatic: >90% excreted in bile, <1% as unchanged drug
- Renal: ~6% <0.1% as unchanged drug
- Major metabolites: AM1, AM4N, AM9

**PROTEIN BINDING**
- 98 to 99%

**USUAL SAMPLING TIMES**
- Pre-dose, normally about 12 or 24 hours after the last dose

**USUAL THERAPEUTIC RANGE**
- Induction therapy (approx. <3 months after transplantation) 150 to 350 µg/l.
- Maintenance therapy: 100 to 250 µg/l.
- Values refer to whole blood specific measurements.
- Therapeutic range varies dependent upon organ transplanted.

**SELECTED FACTORS AFFECTING SERUM CONCENTRATIONS**

**Disease**
- Hepatic impairment reduces cyclosporin clearance and prolongs the elimination half-life
- Diarrhea and inflammatory bowel disorders reduce oral absorption

**Drugs**
- Ketoconazole
- Erythromycin
- Diltiazem
- Verapamil
- Nifedipine
- Rifampicin
- Isoniazide
- Phenytoin
- Phenobarbital
- Carbamazepine

**Notes:**
1. Doses vary widely, depending upon the indication for cyclosporin, the time following transplantation and the co-prescription of other immunosuppressive drugs. It is common practice for cyclosporin dosage to be

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adjusted on the basis of blood concentration measurements. The consensus recommendations are that cyclosporin measurements should be made in blood and the majority of centres follow this advice. Concentrations in plasma or serum are lower and are affected by the temperature of separation of the blood sample.

2. A loading dose is not normally given. A variety of induction protocols are used, some starting cyclosporin before transplantation, others only when adequate renal function has been established, post-operatively. Intravenous doses are usually given in clinical settings in which poor oral absorption is suspected or common. These include after liver transplantation, following bone marrow transplantation and in patients with cystic fibrosis who have received a lung or heart/lung transplant. Oral absorption varies substantially between patients. It may also be affected by bile acids and food. A new oral formulation (Sandimmun Neoral) is available, and appears to display more consistent absorption characteristics than either the current solution or gelatine capsules.

3. The dose is usually reduced on the basis of cyclosporin blood concentration measurements and if there are signs of deteriorating renal function.

4. The intravenous preparation contains polyethoxylated castor oil and has been associated with some adverse reactions, including anaphylaxis. Intravenous doses are approximately one third of the oral dose.

5. Patients with cystic fibrosis may require up-to four times daily dosing because of the relatively large oral doses needed.

6. Blood monitoring prior to steady state may be useful to establish that the patient is absorbing the drug.

7. The elimination half-life may be underestimated if blood samples are only collected during a single 12 or 24 hour dosing interval.

8. Blood samples should not be collected via intravenous lines through which cyclosporin has been administered, as there is significant and reversible binding of the drug to the tubing.

9. Ranges apply primarily to kidney, liver and heart transplant recipients. Higher concentrations are common using the doses associated with lung or heart-lung transplantation. Lower concentrations are common in patients with triple or quadruple regimens and in patients with liver dysfunction. However, there are wide variations in practice between different units.

10. High probability of toxicity at pre-dose concentration > 400 µg/l during maintenance therapy.
References

- Lund L. Arch. Neurol./uniLL44/uniLL4z./uniLL4)/uniLL49
- Oellerich M, Bohm MM, Tietjen HG, Sybrecht GW. Theophyl lines and other methylxanthines, Staib AH, Woodcock BG,