

PHAR 7632 Chapter 17

Metabolism

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Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to describe the various processes by which a drug may be metabolized including Phase 1 and 2 reactions
- be able to describe the role of pharmacogenomics in drug metabolism and drug response
- understand the effect of induction of drug metabolism
- understand the role of inhibition of metabolism on drug interactions
- be able to define the parameters:
 - hepatic clearance
 - hepatic/liver blood flow
 - extraction ratio
 - free intrinsic clearance
- understand the relationship between the parameters hepatic clearance, hepatic blood flow, fraction unbound, and free intrinsic clearance and be able to discuss the venous equilibration model
- be able to discuss the differences between flow limited and capacity limit metabolism/drugs

The body has another way of deactivating drugs in the body. This method of elimination is metabolism or biotransformation. Metabolic processes, in general, have the overall effect of converting drug molecules into more polar compounds. Again, in general, the effect of this should be to decrease tubular re-absorption in the kidney and thus increase drug elimination. Generally, it also means an immediate loss of pharmacological activity because transport into the site of action is hindered (less lipid soluble) or the molecule no longer fits into the receptor site. There are exceptions however, and a number of 'new' drugs have been discovered as active metabolites.

Metabolism takes place by enzymatic catalysis ([by reducing the activation energy of the reaction](#)). Most metabolism occurs in the liver although other sites have been described, such as intestinal wall, kidney, skin, blood. An individual's enzyme activity and concentration in an organ and tissue is can be quite variable, controlled by factors such as age, disease, sex, diet, co-administration of other drugs and genetics. Drugs that are extensively metabolized, where metabolism is a major route of elimination, have considerable between individual variability. With these drugs therapeutic drug monitoring and pharmacogenomics become important considerations.

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Metabolic Processes

Drugs may be metabolized by a wide variety of enzymes located throughout the body. Also, there is a wide variety of reactions that can be called metabolism. These reactions may be grouped into Phase 1 and Phase 2 type reactions. However, some have included Phase 0 and Phase 3 transport processes as part of the overall topic of metabolism.

Commonly there are four types of reactions involved in drug metabolism.

These are:

1. oxidation
2. reduction
3. hydrolysis
-
4. conjugation

The first three are often lumped together as phase I reactions, while the fourth process, conjugation, is called phase II metabolism. A common scheme in the overall metabolism of drugs is that metabolites are metabolized. In particular a drug may be oxidized, reduced or hydrolyzed and then another group may be added in a conjugation step. A common cause of capacity limited metabolism is a limit in the amount of the conjugate added in the conjugation step. Phase 0 and 3.

Phase 0

Phase 0 has been described as the transport of drug from the blood into the hepatocytes in the liver, the [basolateral](#) (sinusoidal) uptake processes ([see Chapter 11](#)) (Ishikawa, 1992).

Although not included in the Phase 0 designation, absorption of drugs from the intestinal lumen to the portal blood supply involves transport and metabolism enzyme processes. The reverse transport enzyme P-glycoprotein (PGP) is often accompanied by the metabolizing enzyme P450 3A (CYP3A). Both of these processes can significantly reduce drug bioavailability and provide a potential for drug interactions (Ritschel and Kearns, 2004).

Phase I

Phase 1 metabolic processes include oxidation, reduction and hydrolysis reactions which typically provide functional groups capable of undergoing Phase 2 reactions. The enzymes which catalyze Phase 1 reactions are found in a number subcellular components including cytoplasm, mitochondria and endoplasmic reticulum. Although the liver is a major organ of metabolism, metabolic enzymes are found throughout the body.

Oxidation

Oxidation is the addition of oxygen and/or the removal of hydrogen. The cytochrome P450 enzymes are the most important of the oxidative enzymes. The cytochrome P450 or CYP family consists of a number of subfamilies such as CYP2C or CYP3A. The individual enzymes are numbered as CYP2C8 or CYP3A4. Hydroxylation is the introduction of an OH group by oxidation. The enzyme CYP3A4 is responsible for the oxidation of dapsone (N-hydroxylation), diazepam (3-hydroxylation), taxol (3'-hydroxylation), warfarin ((S)-4'-hydroxylation) and others. The enzyme CYP2D6 assists in the oxidation of alprenolol, amiodarone (aromatic hydroxylation), debrisoquine (4-hydroxylation), imipramine (2-hydroxylation), propranolol (4-hydroxylation), codeine (O-

demethylation) and others. CYP2C9 is responsible for the oxidation of ibuprofen, phenytoin, tenoxicam, tolbutamide and warfarin (also CYP1A2).

A few examples

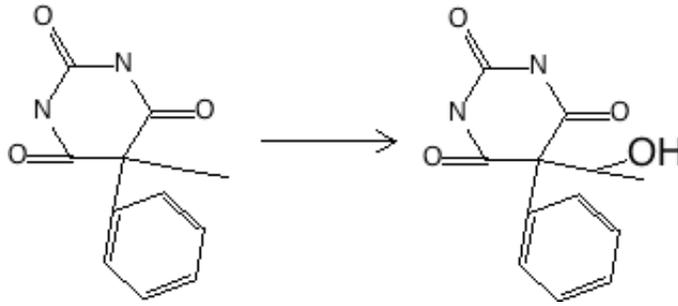


Figure 17.2.1 Aliphatic hydroxylation to alcohol - minor metabolite of phenobarbital

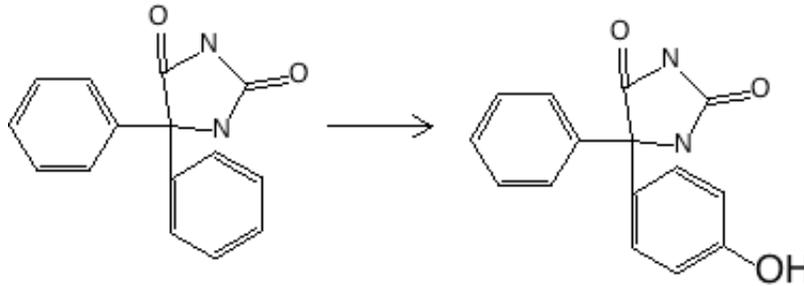


Figure 17.2.2 Aromatic hydroxylation to phenol - major metabolite of phenytoin, *p*-HPPH

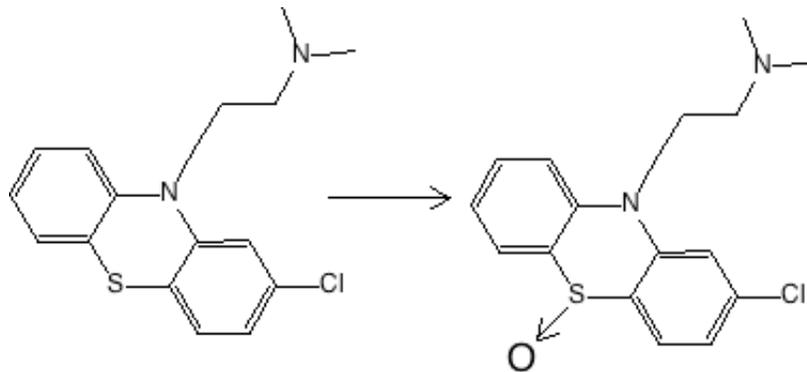


Figure 17.2.3 Oxidation at S (on N) - chlorpromazine to sulfoxide

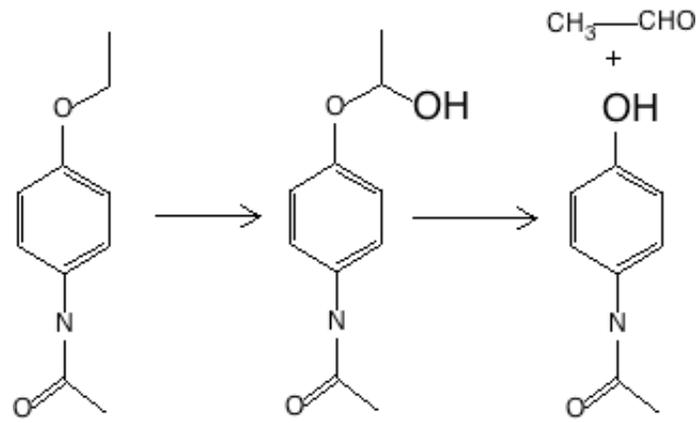


Figure 17.2.4 Two step oxidative dealkylation - phenacetin

Monoamineoxidase

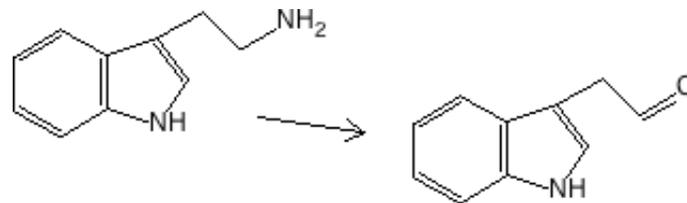


Figure 17.2.5 Oxidation - 5-hydroxytryptamine

Alcohol dehydrogenase - in liver, kidney, lung



Reduction (add H or remove O)

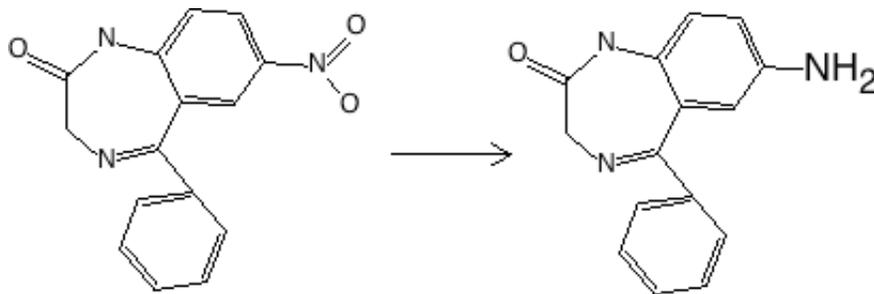


Figure 17.2.7 Reduction of nitro to amine - nitrazepam

Hydrolysis

Addition of water with breakdown of molecule. In blood plasma (esterases) and liver

Esters to alcohol and acid

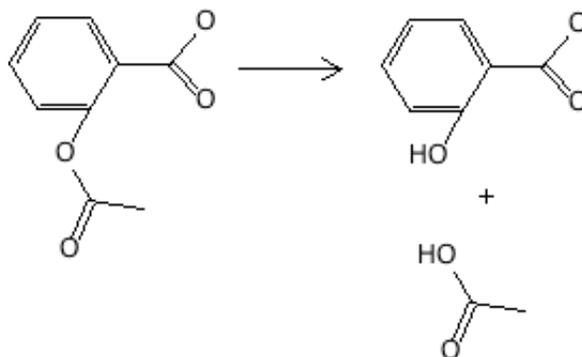


Figure 17.2.8 Hydrolysis - aspirin to salicylic acid

Amides to amine and acid

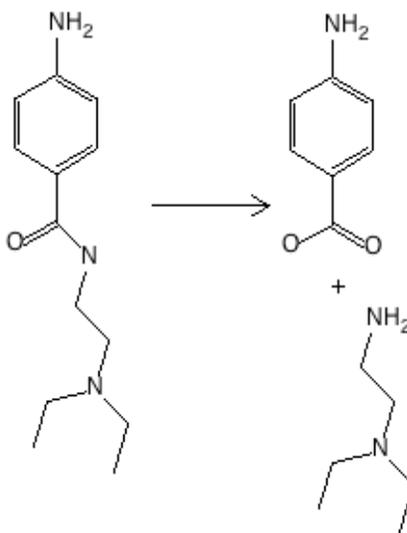


Figure 17.2.8 Hydrolysis - procainamide to *p*-aminobenzoic acid

Phase 2

Conjugation

Conjugation reactions involve the addition of molecules naturally present in the body to the drug molecule. The drug may have undergone a phase I reaction.

Glucuronidation

This is the main conjugation reaction in the body. This occurs in the liver. Natural substrates are bilirubin and thyroxine. Aliphatic alcohols and phenols are commonly conjugated with glucuronide. Thus hydroxylated metabolites can also be conjugated. for example morphine

Acylation

Acylation, especially acetylation with the acetyl group, e.g. sulfonamides

Glycine

Glycine addition ($\text{NH}_2\text{CH}_2\text{COOH}$) for example nicotinic acid

Sulfate

Sulfate ($-\text{SO}_4$) for example morphine, paracetamol

Phase 3

Elimination of the drug or metabolite into bile

Excretion by ATP dependent transporter (e.g. MRP2)

Metabolite is often more Polar

In most cases the metabolite is formed by production of a more polar group, for example $\text{C-H} \rightarrow \text{C-OH}$, or addition of a polar group, for example acetyl (CH_3COO^-). Generally the resultant metabolite is more water soluble, and certainly less lipid soluble. Less drug is reabsorbed from the kidney.

Occasionally the metabolite is less water soluble. A significant example is the acetyl metabolite of some of the sulfonamides. Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria. The earlier answer this was the triple sulfa combination, now the more commonly used sulfonamides have different elimination and solubility properties and exhibit less problems.

Drug as a Pro-drug - Active Metabolite

In most cases the metabolites are inactive, however, occasionally the metabolite is also active, even to the extent that the metabolite may be the preferred compound to be administered. The original drug may take on the role of a pro-drug.

For example:-

amitriptyline ---> nortriptyline

codeine ---> morphine

primidone ---> phenobarbital

Drug metabolism can be quantitatively altered by drug interactions. This alteration can be an increase by induction of enzyme activity or a reduction by competitive inhibition.

Pharmacogenomics - Pharmacogenetics

Pharmacogenomics and the older term pharmacogenetics describe the interaction between drug pharmacokinetics or activity and genetic or genomic parameters. While pharmacogenetics deals with genetic difference between individuals pharmacogenomics deals with the more specific interaction with genes and single nucleotide polymorphisms (SNPs). Genetic polymorphism will cause differences in enzymes, proteins, transporters and receptors.

Responses to Pharmacogenomic Variation

- Alteration in enzyme activity may produce clinically significant differences in drug metabolism.
- Altered protein structure can cause altered drug protein binding
- Changes in drug transporters can alter drug absorption or distribution
- Drug receptor formation is also controlled genetically. Alterations in drug receptors may significantly change drug response.

Some definitions (from [Wikipedia](#) or the references below)

- **Chromosomes** consists of a long strand of deoxyribonucleic acid (DNA). All non reproductive human (diploid) cells contain two pairs of 22 chromosomes plus two sex determining chromosomes for a total of 46. Each
- **DNA** consists of a double chain of deoxyribose, pentose sugar, phosphate group and nitrogenous heterocyclic bases (adenine, cytosine, guanine or thymine). Specific sequences of base pairs in the DNA strands define the gene.
- a **Gene** is a specific section or location of the DNA strand of a chromosome that carries the coding information for some protein or structural RNA. It consists of at least forty base pairs. Genes take up only approximately 1% of a DNA strand of a chromosome. The cells transcribe the genetic information on the gene into RNA and the RNA is translated into a specific protein (enzymes, transporters or receptors). This process is called gene expression. Genetic or mutated variations in the base pair sequence in a gene are alleles also called polymorphism.
- **Alleles** are different forms of a gene. There may be numerous variations of alleles for any gene. The diploid cells contain two copies of each of the 22 non sex chromosomes. The 'normal' or more common allele is called the wild type. Modified or altered alleles may be called mutant. If the allele is copied one copy is inherited from the mother and from the father. If the alleles from each copy are the same the individual is homozygous for that genetic variation. Different alleles mean the individual is heterozygous. There may be many modifications or mutant alleles to an particular gene. Some alleles may be dominant where only one copy is needed for a specific expressions. In other case the allele may be recessive and both copies must be the same (homozygous) for this gene expression. In other cases the heterozygous situation may provide and intermediate expression.

For example consider a gene that determines the activity of a particular enzyme. If there are only two alleles (say A and B), with A being dominant, AA, AB, and BA will produce one (the more common) enzyme activity and only the BB case will provide the alternate enzyme activity. In other cases the two homozygous forms (AA and BB) will produce the extremes of enzyme activity and the heterozygous forms (AB and BA) will produce an intermediate activity. In other cases, there may be many more than two alleles so a wide range of enzyme (protein, transporter or receptor) may be expressed.

Allele naming

- Single nucleotide polymorphisms (SNPs) are alterations in a single base pair at a particular location on the DNA strand of a gene. SNPs may occur at any part of the DNA strand and commonly outside the $\approx 1\%$ that include gene information.

A few examples

- The muscle relaxant succinylcholine is usually rapidly deactivated by plasma butyrylcholinesterase within a few minutes. However, in some individuals genetic variation in the expression of this enzyme results in reduced enzyme activity, reduced metabolism and prolong drug activity. Drug activity may last up to an hour in these individuals (Kalow, 2004).
- During World War II it was observed that some African-American soldiers suffered hemolytic toxicities after usual doses of the anti-malarial primaquine. This was later identified as a higher frequency of genetically controlled lack of the enzyme glucose-6-phosphate dehydrogenase (G6PD) (Kalow, 2004). In a MASH episode ([210 - The Red/White Blues](#)) Max Klinger (played by Jamie Farr), a regular character portraying a soldier of eastern Mediterranean origin also exhibited symptoms of primaquine toxicity which was later attributed to a higher incidence of a genetic deficiency in this population as well.
- Fast and slow acetylators (N-acetyltransferase, NAT) of isoniazid have been identified in varying frequencies in different populations. Normal doses given to slow (unidentified) slow acetylators results in toxicities such as numbness, pain and tingling (Kalow, 2004).
- drug transporters, MDR1
- codeine metabolism to morphine - CYP 2D6

Item 1. It is generally considered that much of the analgesic activity of codeine is due to one of its metabolites, morphine. The O-demethylation of codeine results in measurable, therapeutic concentrations of morphine. This pathway is enzymatically catalyzed by CYP2D6 which has a number of genetically controlled alleles. Thus there are at least extensive (EM) and poor (PM) metabolizers of codeine. There are reports of intermediate and also poor intermediate metabolizers as well. PM produces almost no morphine and thus codeine is ineffective in these individuals. Thus, the concentration of morphine and its therapeutic efficacy is greatly reduced in PM.

[Explore this problem as a Linear Plot - Java Applet](#)

References

- Kwon, Y. 2001 **Handbook of Essential Pharmacokinetics, Pharmacodynamics and Drug Metabolism for Industrial Scientists**, Chapter 8 Metabolism, Kluwer Academic, New York
- Ritschel, W.A. and Kearns, G.L. 2004 **Handbook of Basic Pharmacokinetics ... including Clinical Applications**, 6th ed., American Pharmaceutical Association, Washington, DC ISBN 1-58212-054-4
- Humma, L.M., Ellingrod, V.L. and Kolesar, J.M. 2003 **Lexi-Comp's Pharmacogenomics Handbook**, Lexi-Comp, Hudson, OH ISBN 1-59195-060-0
- Ishikawa T. 1992 The ATP-dependent glutathione S-conjugate export pump. *Trends Biochem Sci*, pp463-468
- Licinio, J. and Wong, M.-L. 2002 **Pharmacogenomics**, Wiley-VCH, Weinheim, Germany ISBN 3-527-30380-4
- Vavricka, S.R. et al. 2002 Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver, *Hepatology*, Jul **36**(1), pp164-72
- Kalow, W. 2004 Pharmacogenetics: A Historical Perspective in **Pharmacogenomics: Application to Patient Care**, Amer. College Clin. Pharmacy, Kansas, MO ISBN 1-880401-80-0
- [P450 - Drug Table](#)
- [Another P450 - Drug Table](#)
- [Cytochrome P450 \(CYP\) Allele Nomenclature Committee](#)
- [P450, UGT and P-gp Drug Interactions](#)
- FDA [Guidance for Industry Pharmacogenomic Data Submissions \(22 Mar 2005\)](#) and [attachment \(22 Mar 2005\)](#)

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Metabolism

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Induction and Inhibition

Metabolism based drug-drug and other interactions can have a significant influence on the use and safety of many drugs. Induction of drug metabolism can lead to unexpected drops in drug concentration or the build-up of metabolites. The reverse can occur when there is inhibition of drug metabolism.

Induction

Enzyme induction is an increase in enzyme concentration caused by a drug or environmental compound. Induction may result from transcriptional activation (more common with CYP450 enzymes) or enzyme stabilization. A number of drugs can cause an increase in liver enzyme activity over time. This in turn can increase the metabolic rate of the same or other drugs. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc. Carbamazepine is another drug which can induce its own metabolism. Rifampin has been shown to cause up to a twenty times increase in midazolam metabolism. Cigarette smoking can cause increased elimination of theophylline (two fold increase) and other compounds. Dosing rates may need to be increased to maintain effective plasma concentrations.

Inhibition

Understanding drug inhibition potential is an important part of any new drug development. One preparation used in these studies are cDNA expressed CYP450 enzymes. Human liver microsomes may also be used for a broader enzyme exposure. Inhibition may be competitive (inhibitor binds to free enzyme), uncompetitive (inhibitor binds to enzyme-substrate complex), noncompetitive (inhibitor and substrate bind to different sites on the enzyme) or mixed. The parameters, K_i (inhibitory constant - the concentration of inhibitor that increases the 'apparent' K_m twofold) and IC_{50} (inhibitor concentration causing a 50% inhibition) can be determined with these *in vitro* systems.

A number of drugs can inhibit the metabolism of other drugs. An example is the 1998 withdrawal from the market of the drug mibefradil (Posicor[®]). Shortly after the 1997 FDA approval of this drug it was found to be a potent metabolic inhibitor of drugs such as simvastatin and other statins, cyclosporin and terfenadine resulting in serious toxicities. Warfarin inhibits tolbutamide elimination which can lead to the accumulation of drug and may require a downward adjustment of dose. Grapefruit juice has been shown to cause a two-fold increase in saquinavir AUC and reduced (inhibited) metabolism of other drugs such as midazolam and coumarin.

Item 1. Metabolism can be subject to a number of factors, such as genetics, disease state and co-administration of other compounds. Other compounds may inhibit metabolism or induce metabolic activity. Some drugs are capable of inducing their own metabolism.

Carbamazepine is a drug which can induce its own metabolism during the first few days of therapy (Hawkins Van Tyle and Winter, 2004). After the first dose, carbamazepine pharmacokinetic parameters include $F = 0.8$, $V = 1.4$ L/hr, $Cl = 0.028$ L/Kg/hr. After 3 to 5 days carbamazepine metabolism is induced such that the Cl becomes 0.064 L/Kg/hr. For a 70 Kg patients pre-induction (first-dose) parameter values are $k_{el} = 0.02$ hr⁻¹ and $V = 100$ L. After induction the k_{el} changes to 0.045 hr⁻¹. Dose adjustment during the first few days can be difficult. Using post induction parameters for initial dosage regimen could cause toxic concentrations. For example, try the simulation again with a dose regimen of 600 mg every 12 hours with both pre and post induction k_{el} values. The typical therapeutic plasma concentration range is 4 - 12 mg/L. [Explore the problem as a Linear Plot - Java Applet](#)

Item 2. Theophylline has been studied extensively. It has been used commonly and has been the subject of therapeutic drug monitoring (TDM) because of its variable pharmacokinetic parameters and narrow therapeutic window. Theophylline parameter values vary considerably with disease state, enzyme status (drug co-administration or smoker status) and formulation factors.

Theophylline is marketed in a number of oral dosage forms. Rapid release tablets generally are rapidly and completely absorbed with F close to 1.0 and k_a values above 2 hr^{-1} . The apparent volume of distribution is approximately 0.5 L/Kg (ideal body weight, IBW). Average values of theophylline clearance approximate 0.04 L/Kg/hr (based on IBW). A number of factors can influence this average clearance value. For example; smoking $\times 1.6$, cimetidine co-administration $\times 0.6$, phenytoin co-administration $\times 1.6$, congestive heart failure $\times 0.5$ (depending on status), cystic fibrosis $\times 1.5$, hepatic cirrhosis $\times 0.5$. Considering a 70 Kg (IBW) non-smoker patient the expected V and k_{el} might be 35 L and 0.08 hr^{-1} . For a patient that smokes the k_{el} would be expected to be approximately 0.125 hr^{-1} . Try adjusting the parameter values according to these covariates and adjust the dosing regimen to maintain appropriate therapeutic concentrations. Currently, the therapeutic window ranges from 5 to 20 mg/L whereas earlier a range of 10 to 20 mg/L had been used. Average plasma concentration targets includes values around 10 mg/L or in the range 8 to 15 mg/L (Aminimanizani and Winter, 2004). [Explore the problem as a Linear Plot - Java Applet](#)

References

- Krishna, R. 2004 **Applications of Pharmacokinetic Principles in Drug Development**, Kluwer Academic/Plenum Publishers, New York, NY ISBN 0-306-47766-1
- Bonate, P.L. and Howard, D.R., ed. 2004 **Pharmacokinetics in Drug Development: Clinical Study Design and Analysis**, Volume 1, AAPS Press, Arlington, VA ISBN 0-9711767-4-4
- Shargel, L. and Yu, A.B.C. 1999 **Applied Biopharmaceutics and Pharmacokinetics**, 4th ed., Appleton & Lange. Stamford, CT ISBN 0-8385-0278-4
- Aminimanizani, A. and Winter, M.E. 2004 Chapter 12 "Theophylline" in **Basic Clinical Pharmacokinetics**, 4th ed., Winter, M.E., Lippincott Williams & Wilkins, Baltimore, MD

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Hepatic Clearance

The systemic clearance, CL, is a measure of the efficiency with which a drug is irreversibly removed from the body. Under first order conditions, clearance can be calculated as:

Single dose

$$CL = \frac{F \bullet Dose}{AUC} = \frac{0.693 \bullet V_{area}}{t_{1/2}}$$

Equation 17.4.1 Clearance after a Single Dose

During multiple dose regimens, clearance can be calculated under steady state conditions as:

$$CL = \frac{k_0}{Cp^{ss}} = \frac{F \bullet Dose}{Cp \bullet \tau}$$

Equation 17.4.2 Clearance at Steady State

where Cp^{ss} is the steady state plasma concentration and Cp is the average plasma concentration during the dosing interval τ .

Venous equilibration model equation

The above equations apply to the overall clearance of drug from the body. We can also consider the organ clearance as it may be measured in an isolated organ system. Here we would have for example an isolated liver, perfused with blood containing the drug of interest. By measuring the drug concentration in the blood entering and leaving the organ at steady state, the organ clearance can be measured for the drug.

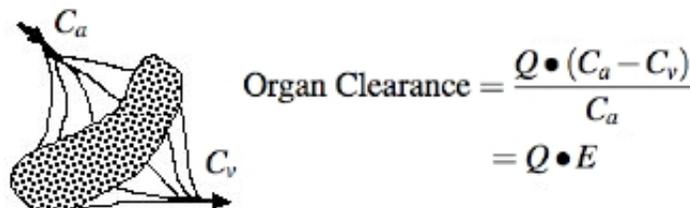


Diagram 17.4.1 Blood Flow through the Liver

where Q is the blood flow rate to the organ, C_a is the concentration of drug in the blood entering the organ, and C_v is the concentration of drug in the blood leaving the organ. The term E is the steady state **extraction ratio**. High E values mean high clearance by the liver and thus extensive metabolism.

The sum of the individual organ clearance values are equal to the systemic clearance, CL. For a drug which is eliminated entirely via

the liver, the hepatic clearance is equal to the systemic or total body clearance. From the equation above we can see that the organ clearance is a function of the liver blood flow and the extraction ratio of the drug. The liver blood flow is a physiological parameter which may be altered in disease states. The extraction ratio, we shall see shortly is a parameter dependent not only of the condition of the liver but also the drug.

Both the hepatic clearance and the extraction ratio are empirical parameters which can be used as measures of the efficiency of the elimination process. They are dependent on three independent variables:-

1. total hepatic blood flow (Q),
2. fraction unbound (fu) or the extent of drug binding to blood constituents. This may be saturable with high dose, polar compounds, and
3. the free intrinsic clearance (CL_{int}) or the rate-limiting step in drug uptake from blood, intracellular transport, metabolism, and where necessary biliary secretion. The free intrinsic clearance may be thought of as the clearance of drug from liver plasma water, devoid of the influence of blood flow or binding. Since a major part of this parameter is metabolism which is typically enzyme mediated this parameter may be saturated at higher doses, for some drugs

The equation describing hepatic clearance in terms of these parameters using the venous equilibration model can be defined as (Wilkinson and Shand 1975):-

$$CL = Q \cdot \frac{fu \cdot CL_{int}}{(Q + fu \cdot CL_{int})} = \frac{Q \cdot CL_{int}^{total}}{Q + CL_{int}^{total}}$$

Equation 17.4.3 Clearance

$$\text{with } E = \frac{fu \cdot CL_{int}}{(Q + fu \cdot CL_{int})}$$

$$CL = Q \cdot E$$

With this equation it is possible to look at the influence of free intrinsic clearance, drug binding, and liver blood flow on the overall hepatic clearance of a drug. Drugs can be classified into three types depending on the intrinsic clearance and binding. Flow limited, capacity limited, and others.

Flow limited drugs

High $fu \cdot CL_{int}$ (= CL_{int}^{total}) value. [$fu \cdot CL_{int} \gg Q$]. For drugs with high total intrinsic clearance the extraction ratio, E , approaches 100%, the hepatic clearance approximates and is dependent of hepatic blood flow. Hepatic clearance is said to be **FLOW LIMITED**. Also, we can note that the hepatic clearance is not dependent on moderate changes in free intrinsic clearance or binding to blood constituents.

$$CL = Q \cdot \frac{fu \cdot CL_{int}}{fu \cdot CL_{int}} = Q$$

Examples include:- lidocaine, propranolol, morphine.

Capacity limited drugs

Very low total intrinsic clearance. [$fu \cdot CL_{int} \ll Q$]. With drugs having very low intrinsic clearance, hepatic extraction is inefficient and hepatic clearance becomes independent of hepatic blood flow. Now changes in free intrinsic clearance and/or binding to blood constituents becomes very important in determination of the overall hepatic clearance. Hepatic clearance is said to be **CAPACITY**

LIMITED as the intrinsic capacity of the liver controls the drug clearance.

$$CL = Q \cdot \frac{fu \cdot CL_{int}}{Q} = fu \cdot CL_{int}$$

Examples include:- phenytoin, warfarin, and quinidine. For such drugs it is possible that liver disease will cause a decrease in CL_{int} but also an increase in fu . In this case the overall hepatic clearance doesn't reflect just the hepatic metabolic activity but also the drug binding. This is illustrated with tolbutamide. In patients with hepatitis there is an increase in fu but no change in CL_{int} . As a result CL is increased and the elimination half-life decreases. The change in elimination half-life reflects changes in binding and not changes in drug metabolizing activity.

Other drugs

Between these two extremes. Capacity-limited but binding-insensitive drugs. The three parameters; Q , fu , and CL_{int} are important determinants of drug elimination.

Examples include:- theophylline, antipyrine

References

- Wilkinson, G.R., and Shand, D.G. 1975 **A physiological approach to hepatic drug clearance**, *Clin. Pharmacol. Ther.*, **18**, 377-90

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Systemic Availability

Even if we can assume that a drug is completely absorbed across the G-I tract, a proportion of the dose may be eliminated by the liver before reaching the systemic circulation because of the anatomical arrangement of the portal circulation. This pre-systemic or **first-pass** elimination can be determined from the extraction ratio, E, such that the fraction of the dose that is available to the central circulation is 1-E. This 1-E value becomes the maximum availability possible before allowing for reduced product performance.

For drugs which are extensively metabolized, first pass metabolism can be quite important. It means that higher doses must be given orally compared with parenteral administration.

For example morphine PO 30 mg, cf. IV 5 mg

and lidocaine not active PO

In liver disease there is potential for changing the systemic availability of high extraction drugs and thereby affecting steady state concentrations.

If liver disease causes a modest reduction in the extraction ratio, from for example 0.95 to 0.9, the fraction of the orally administered drug reaching the systemic circulation (1-E) will be doubled. One of the consequences of the pathogenesis of chronic liver disease is the development of porta-systemic shunts that may carry drug absorbed from the G-I tract through the mesenteric veins directly into the systemic circulation. Thus in a disease where biochemical hepatic function is relatively well maintained (e.g., schistosomiasis), oral treatment with high clearance drugs such as **morphine or propranolol** can lead to high blood levels and an increase in adverse drug effects. For example, 30 mg morphine orally may act like 30 mg IV and lead to over dosage toxicity.

Pharmacokinetics of Drugs in Patients with Liver Disease

Liver disease can have a profound effect on the patient's physiology which in turn can influence drug pharmacokinetics. Using the venous equilibration model presented on the previous page we can expect changes in f_u , Q and CL_{int} to influence the overall pharmacokinetics of a drug. This can be due to changes in protein binding (Chapter 18), to reduced enzymatic activity of the liver cells or reduced ability of the drug to reach the enzymes present in liver cells.

Decreased protein binding appears to be more common in chronic liver disease (such as cirrhosis) compared with more acute diseases (such as viral hepatitis). Some examples include morphine (15%), propranolol (38%), diazepam (70-200%), phenytoin (40%) and tolbutamide (30%) (Benet et al. 1984 t70).

A number of high extraction ratio (flow limited) drugs exhibit increased oral bioavailability, decreased clearance or increased half-life. Some examples include chlormethiazole (F increased 1000% and decreased clearance), lidocaine (decreased clearance), meperidine (increased F and $t_{1/2}$ with decreased clearance), propranolol (increased F and $t_{1/2}$) and verapamil (increased F and $t_{1/2}$ and decreased clearance) (Benet et al. 1984 t67).

Capacity limited (poorly extracted) drugs also have altered pharmacokinetic parameters in patients with liver disease. Examples include ampicillin (increased $t_{1/2}$), diazepam (increased $t_{1/2}$ and decreased clearance), theophylline (increased $t_{1/2}$ and decreased clearance) and tolbutamide (increased $t_{1/2}$ and decreased clearance) (Benet et al. 1984 t68-9).

Pharmacogenomic Considerations

Enzymes are produced according to the genetic make-up of the individual. This means that different individuals may produce more or less of a particular enzyme but it also means that different forms (allele variants) of the enzyme may be produced by different individuals. Enzymes control the metabolism of many drugs and different forms of these enzymes will cause differences in the pharmacokinetics of the drugs. Some enzymatic forms are more active, others less active. One example is the enzyme CYP2C9 and its influence on warfarin pharmacokinetics (that is, the five times more active S-form). There are three forms of CYP2C9; *1, *2 and *3. The CYP2C9*1 is the wild form and the most common. However, there are 10% and 8% of population with the *2 and *3 forms, respectively. Both these variants result in reduced enzymatic activity or reduced drug clearance. One study (Higashi et al 2002) indicated that the daily maintenance dose ranged from 5.6 mg (*1/*1) to 1.6 mg (*3/*3) with different individuals. These studies suggest the potential for more difficult stabilization of the required dose and higher incidence of bleeding.

- Genotyping can be performed by relatively sophisticated (expensive) techniques which should become more affordable and common in the future.
- Another approach is the use of a test compound to determine CYP2C9 (or other enzyme) activity in an individual. For CYP2C9, compounds such as diclofenac, phenytoin, tolbutamide and S-warfarin have been considered (Ritschel and Kearns, 2004 p359).
- A third approach is to recognize this potential for genetic (and other) sources of variability and carefully monitor the initial doses of the therapeutic compound, that is, apply therapeutic drug monitoring (TDM).

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References

- Humma, L.M., Ellingrod, V.L., and Kolesar, J.M. 2003 **Lexi-Comp's Pharmacogenomics Handbook**, Lexi-Comp, Hudson, OH ISBN 1-59195-060-0
- Higashi, M.K., Vennestra, D.L., Kondo, L.M., Wittkowsky, A.K., Srinouanprachanh, S.L., Farin, F.M. and Rettie, A.E. 2002 "Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy, *J. Amer. Med. Assoc.*, **287**(13), 1690-98
- Benet, L.Z., Massoud, N. and Gambertoglio, J.G. 1984 **Pharmacokinetic basis for drug treatment**, Raven Press, New York, NY ISBN 0-89004-874-6
- Ritschel, W.A. and Kearns, G.L. 2004 **Handbook of Basic Pharmacokinetics**, 6th ed., APhA, Washington, DC ISBN 1-58212-054-4

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