Introduction to Drug Metabolism

Reference Sources

- The Pharmacological Basis of Therapeutics
  Goodman and Gilman
  (lot of info, not cheap)
- Introduction to Drug Metabolism
  Gibson and Skett
  (lots of metabolism info, cheap)

Sources of Additional Info

- http://www.bhcs.com/proceedings/13_4/13_4_ogu.htm
- http://www.theberries.ns.ca/Archives/cyp450.html
- http://www.hospitalist.net/highligh.htm
- http://www.pharmacy.umaryland.edu/~umdi/grape.htm
- http://www.pharmacy.umaryland.edu/~umdi/grape.htm

Where are we?

- Absorption- drug gets into bloodstream
- Distribution - gets to site of action
- Metabolism - is “changed” so that it can be excreted
- Elimination - leaves the body

Lipophilic Nature allows

passage through biological membranes

access to site of action

BUT hinders excretion

Renal Excretion

- Renal excretion of unchanged drug plays small role in elimination of drug
- In the kidney, lipophilic compounds are largely reabsorbed back into systemic circulation during passage through renal tubules
- Needs to be water soluble (hydrophilic)

Metabolism

- The metabolism of drugs and other xenobiotics into more hydrophilic metabolites is essential for the elimination of these compounds from the body and termination of their biological activity.

Biotransformation

- Generates more polar (water soluble), inactive metabolites
- Readily excreted from body
- Metabolites may still have potent biological activity (or may have toxic properties)
- Generally applicable to metabolism of all xenobiotics as well as endogenous compounds such as steroids, vitamins and fatty acids

Phase I and Phase II Metabolism

- Phase I
  - functionalization reactions
- Phase II
  - conjugation reactions

Phase I

- Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH).
- Usually results in loss of pharmacological activity
- Sometimes may be equally or more active than parent

Prodrug

- Pharmacologically inactive
- Converted rapidly to active metabolite (usually hydrolysis of ester or amide bond)
- Maximizes the amount of active species that reaches site of action

Phase II (conjugation reactions)

- Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid
- Highly polar – rapidly excreted in urine and feces
- Usually inactive - notable exception is morphine 6-glucuronide

Site of Biotransformation

- Enzymatic in nature
- Enzyme systems involved are localized in liver
- Every tissue has some metabolic activity
- Other organs with significant metabolic capacity are gi tract, kidneys and lung

First-Pass Metabolism

- Following nonparenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the intestinal endothelium or the liver before it reaches the systemic circulation

- Limits oral availability of highly metabolized drugs

Endoplasmic Reticulum (microsomal) and Cytosol

With respect to drug metabolizing reactions, two sub cellular organelles are quantitatively the most important: the endoplasmic reticulum and the cytosol.

The phase I oxidative enzymes are almost exclusively localized in the endoplasmic reticulum.

Phase II enzymes are located predominantly in the cytosol.

Phase I Metabolism

Includes oxidation, reduction, hydrolysis, and hydration and isomerization (plus rarer misc.)

- Many drugs undergo a number of these reactions
- Main function of Phase I metabolism is to prepare the compound for phase II metabolism
- Mixed function enzyme system found in microsomes of many cells (esp liver, kidney, lung, intestine) performs many different functionalization reactions

Cytochrome P450 Monooxygenase System

- Superfamily of heme containing proteins
- Involved in metabolism of diverse endogenous and exogenous compounds
  - Drugs
  - Environmental chemicals
  - Other xenobiotics

Cytochrome P450 Nomenclature and Multiple Forms

- ~1000 currently known cytochrome P450s, about 50 active in humans

- Basis of nomenclature system is divergent evolution – sequence similarity between the cytochrome P450s

- categorized into 17 families (CYPs)
  - sequences > 40% identical
  - identified by Arabic number, CYP**1**, CYP**2**
- further into subfamilies
  - sequences >55% identical
  - identified by a letter, CYP1**A**, CYP2D
- may have different, individual isoforms
  - identified by another Arabic number, CYP2D**6**, CYP3A**4**

These are the types of reactions performed by the Cytochrome P450 system

• Aromatic hydroxylation	Phenobarbital, amphetamine
• Aliphatic hydroxylation	Ibuprofen, cyclosponine
• Epoxidation	Benzo [a] pyrene
• N-Dealkylation	Diazepam
• O- Dealkylation	Codeine
• S- Dealkylation	6-Methylthiopurine
• Oxidative Deamination	Diazepam, amphetamine
• N-Oxidation	Chlorpheniramine
• S-Oxidation	Chlorpromazine, cimetidine
• Phosphothionate oxidation	Parathion
• Dehalogenation	Halothane
• Alcohol oxidation	Ethanol

Phase I Metabolism Summary

Virtually every possible chemical reaction that a compound can undergo can be catalyzed by the drug metabolizing enzyme systems

- The final product usually contains a chemical reactive functional group OH, NH2, SH, COOH.
- This functional group can be acted upon by the phase II or conjugative enzymes.
- Main function of Phase I metabolism is to prepare the compound for phase II metabolism, not excretion.

Phase II Metabolism

- Phase II is usually the true detoxification of drugs
- Occurs mostly in cytosol
- Gives products that are generally water soluble and easily excreted
- Includes sugar conjugation, sulfation, methylation, acetylation, amino acid conjugation, glutathione conjugation

Glucuronidation

- Most widespread, important of the conjugation reactions
- Cofactor *UDP – glucuronic* acid is in high abundance
  - Closely related to glycogen synthesis
  - Found in all tissues of the body
- Other sugars, glucose, xylose or ribose may be conjugated

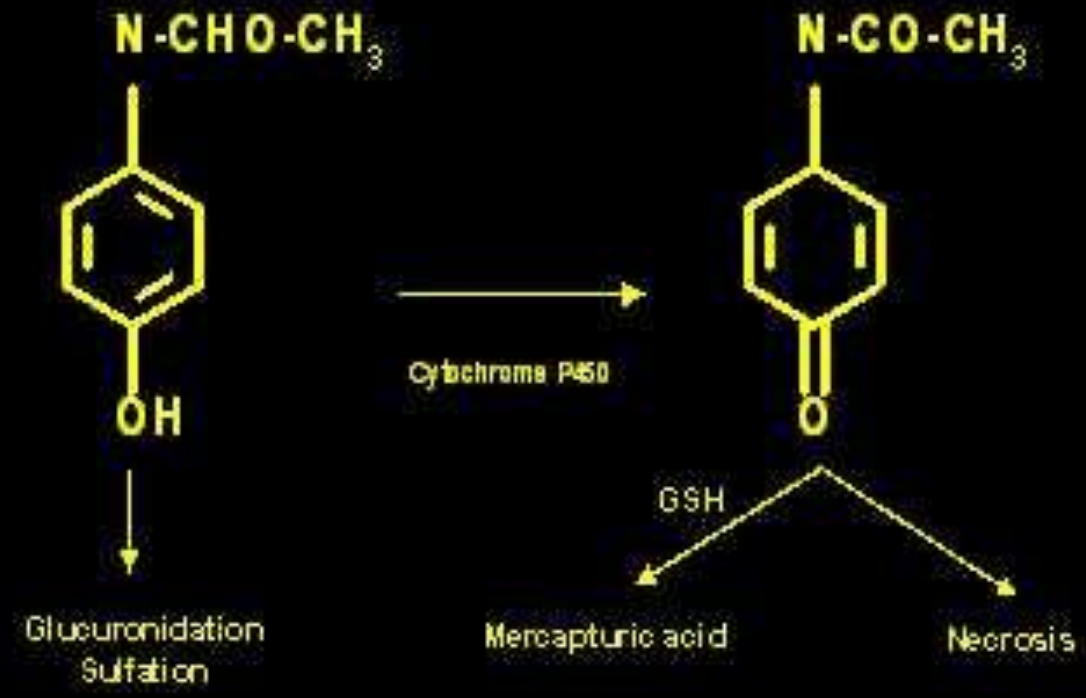
Sulfation

- Major conjugation pathway for phenols, also alcohols and amines
- Compounds that can be glucuronidated can also be sulfated
- Can be competition between the two pathways
- In general, sulfate conjugation predominates at low substrate concentration and glucuronide conjugation predominates at high substrate concentration

Glutathione Conjugation

- Glutathione is a protective compound (tripeptide, Gly-Cys-Glu) within the body for removal of potentially toxic electrophilic compounds
- Many drugs are, or are metabolized in phase I to, strong electrophiles
- React with glutathione to form non- toxic conjugates
- Glutathione conjugates may be excreted directly in urine or bile, but are usually metabolized further

METABOLISM OF ACETAMINOPHEN



Stereoselective Reactions

- Many drugs in use are optically active
- Optical isomers of many drugs are metabolized differently

Warfarin exists as R- and S-isomers, the S isomer disappears from the plasma at a faster rate than the R isomer

Factors affecting Drug Metabolism

- Environmental Determinants
  - Induction
  - Inhibition
- Disease Factors
- Age and Sex
- Genetic Variation

Environmental Determinants

- Activity of most drug metabolizing enzymes can be modulated by exposure to certain exogenous compounds
  - Drugs
  - Dietary micronutrient (food additives, nutritional or preservative)
  - Environmental factors (pesticides, industrial chemicals)
- Can be in the form of induction or inhibition
- Contributes to interindividual variability in the metabolism of many drugs

Induction of Drug Metabolism

Enzyme induction is the process by which exposure to certain substrates (e.g., drugs, environmental pollutants) results in accelerated biotransformation with a corresponding reduction in unmetabolized drug.

(some substance stimulates the synthesis of the enzyme and the metabolic capacity is increased -drug gets metabolized faster)

Induction of Drug Metabolism

- Many currently used drugs are well known to induce their own metabolism or the metabolism of other drugs. Some examples are the anticonvulsant medications phenobarbital and carbamazepine, and even St. John's Wort.
- Cigarette smoking can cause increased elimination of theophylline and other compounds.

Consequences of Induction

- Increased rate of metabolism
- Decrease in drug plasma concentration
- Enhanced oral first pass metabolism
- Reduced bioavailability
- If metabolite is active or reactive, increased drug effects or toxicity

Therapeutic Implications of Induction

- Most drugs can exhibit decreased efficacy due to rapid metabolism
  - but drugs with active metabolites can display increased drug effect and/or toxicity due to enzyme induction
- Dosing rates may need to be increased to maintain effective plasma concentrations

Inhibition of Drug Metabolism

- Drug metabolism is an ***enzymatic process*** can be subjected to inhibition.
- Drugs and other substances can inhibit the metabolism of other drugs.

Some types of inhibition

- Competition between substrates for enzyme active site

  Concentration of substrates

  Affinity for binding site (drug with hi affinity for an enzyme will slow the metabolism of any low affinity drug)
- Irreversible inactivation of enzyme

  Complex with heme iron of CYP450 (cimetidine, ketoconazole)

  Destruction of heme group (secobarbital)
- Depletion of cofactors such as NADH2 for phase II enzymes

Consequences of Inhibition

- Increase in the plasma concentration of parent drug
- Reduction in metabolite concentration
- Exaggerated and prolonged pharmacological effects
- Increased liklihood of drug-induced toxicity

Therapeutic Implications of Inhibition

- May occur rapidly with no warning
- Particularly effects drug prescribing for patients on multidrug regimens
- Knowledge of the CYP450 metabolic pathway provides basis for predicting and understanding inhibition

Esp drug drug interaction

http://www.hospitalist.net/highligh.htm

CYP1A2 Affected Drugs, Inducers, and Inhibitors

Affected Drugs	Inducers	Inhibitors
Tricyclicantidepressants Propranolol F-Warfarin Theophylline	Omeprazole (Prilosec) Phenobarbital Phenytoin Rifampin Smoking Char-broiled meats	Quinolone antibiotics, esp. ciprofloxacin Grapefruit juice

Note: CYP1A2 is the only isoform known to be affected by tobacco smoking. Example: smoking induces formation of CYP1A2 enzymes causing smokers to require higher doses of theophylline than non-smokers.

Disease Factors

Liver Disease – Cirrhosis, Alcoholic liver disease, jaundice, carcinoma

- *Major location of drug metabolizing enzymes*
- *Dysfunction can lead to impaired drug metabolism- decreased enzyme activity*
- *First pass metabolism effected – may inc 2-4 x bioavailiability*
- *Results in exaggerated pharmacological responses and adverse effects*

Cardiac failure causes decreased blood flow to the liver

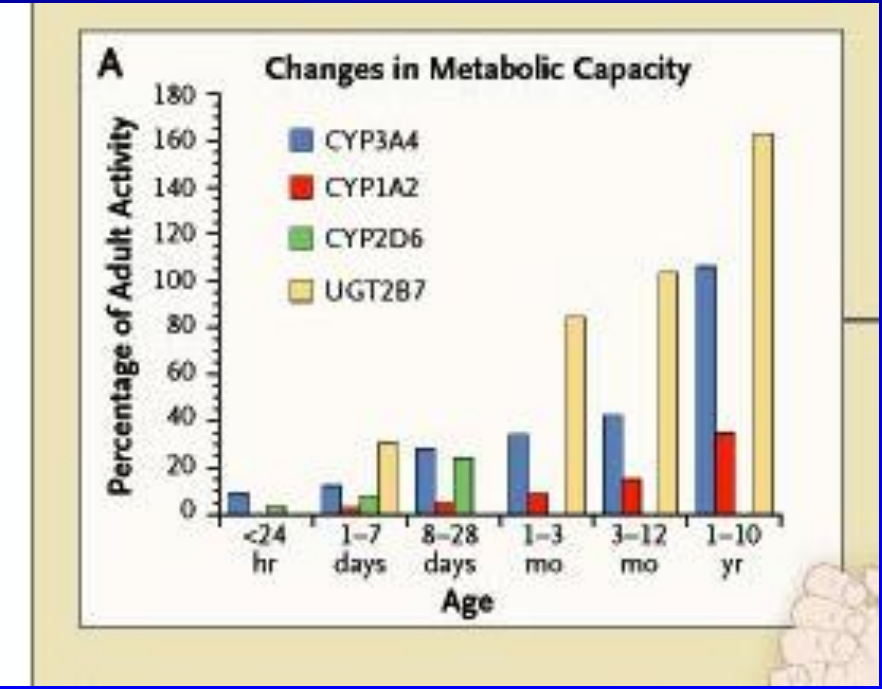
Hormonal diseases, infections and inflammation can change drug metabolizing capacity

Age

- Newborns and infants – metabolize drugs relatively efficiently but at a rate generally slower than adults
- Full maturity appears in second decade of life
- Slow decline in function associated with aging

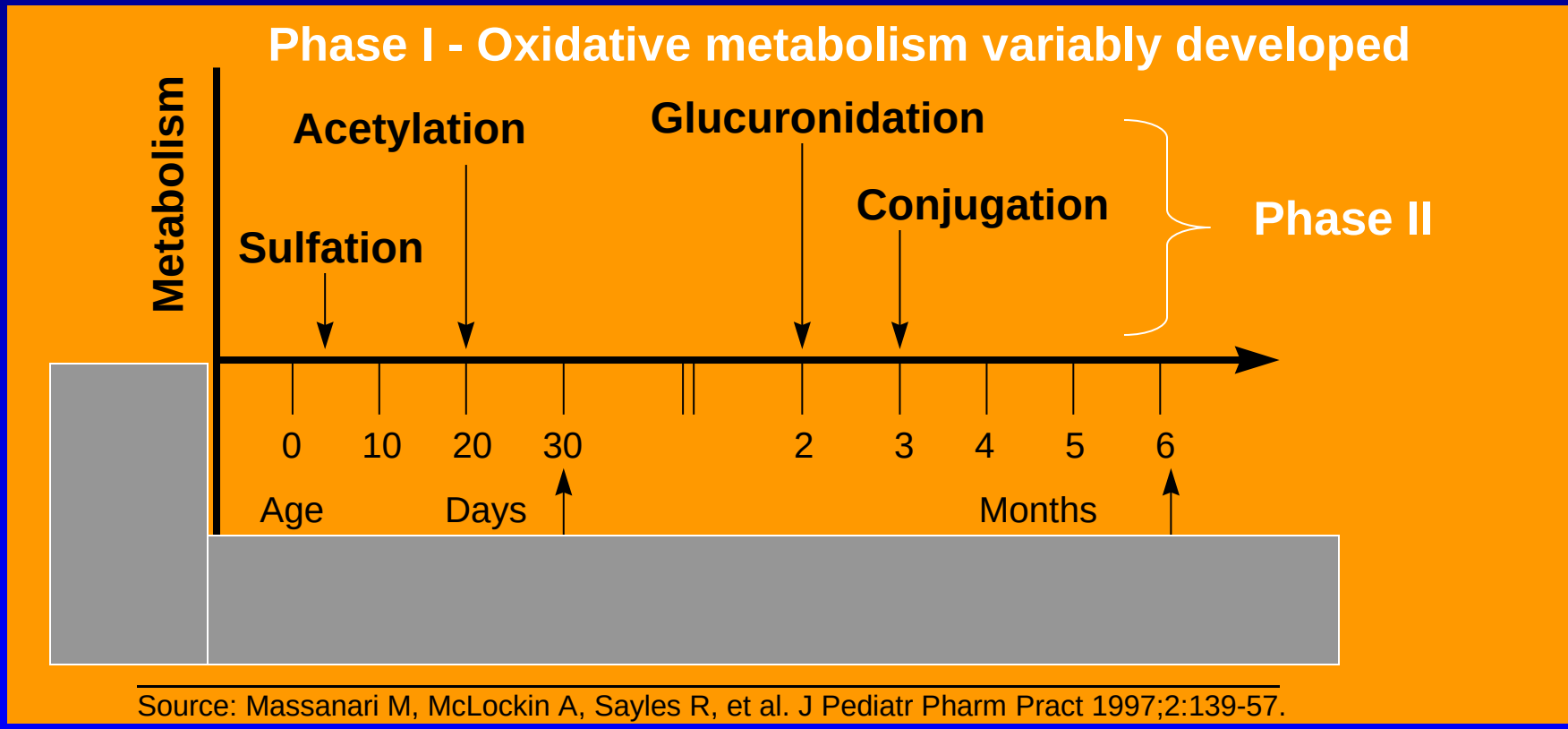
Developmental Changes in Physiologic Factors That Influence Drug Disposition in Infants, Children, and Adolescents

Oxidative Metabolic Capacity as Function of Age



Kearns G et al. N Engl J Med 2003;349:1157-1167

Metabolism



Source: Massanari M, McLockin A, Sayles R, et al. J Pediatr Pharm Pract 1997;2:139-57.

Metabolism

Premature neonates

Phase I Oxidative

Phase II Conjugate

Pathway	Status of development	Medications affected
Oxidation	impaired	theophylline phenobarbital phenytoin diazepam
Sulfation	well-developed	
Glucuronidation	not developed	chloramphenicol **acetaminophen** morphine

Infants

1. liver is large in size relative to body
2. in neonate metabolic capacity of liver is 50% of that in adult
3. liver function matures during first 6 months of life

Metabolism
Pediatric Considerations

Variable	Age Group	Result	Examples
Dec. enzyme capacity	Neonates, young infants	Inc t ½ ; dec clearance	Phenobarbital
Inc. enzyme capacity	Children	Dec t ½; Inc. clearance	Theophylline

Sex

- Responsiveness to certain drugs is different for men and women
- Pregnancy – induction of certain drug metabolizing enzymes occurs in second and third trimester
- Hormonal changes during development have a profound effect on drug metabolism

Genetic Variation

http://www.private-rx.co.uk/invivo/pharmacogenetics.shtml

- wide variability in the response to drugs between individuals
- consequences of such variation may be therapeutic failure or an adverse drug reaction
- genetic diversity is the rule rather than the exception with all proteins, including drug metabolizing enzymes

- allelic variants with different catalytic activities from that of the wild-type form have been identified
- inheritance leads to subpopulations (genetic polymorphisms) with different drug metabolizing abilities

  lack of activity

  reduction in catalytic ability

  enhanced activity
- frequency of the polymorphism often varies according to the ethnic ancestry of the individual

- CYP2D6 is extensively studied, the gene for CYP2D6 is highly polymorphic
- It's expression leads to 3 phenotypes (phenotype is the expression of genetic make-up)

  Extensive metabolizers (EMs) have functional enzyme activity

  Intermediate metabolizers (IMs) have diminished enzyme activity

  Poor metabolizers (PMs) have little or no activity
- 5-10% of Caucasians and 1-2% of Asians exhibit the PM phenotype

- Debrisoquine, formerly used in the treatment of hypertension, is metabolized by CYP2D6 to 4-hydroxydebrisoquine
- Remarkable interindividual variation in pharmacological effect of the drug
- Urine of volunteers given debrisoquine was examined for presence of 4-hydroxydebrisoquine
  - One subject had a very low conversion of parent drug to metabolite
  - was very sensitive to the antihypertensive effects of debrisoquine

- Drugs linked to this phenotype should be given in lower doses to PM individuals than EM to reduce risk of overdose and toxic effects.

On the other hand

- Codeine is oxidized to morphine by CYP2D6
  - necessary for codeine's analgesic effect
  - PMs may have no therapeutic effect

And now, back to the patient?

Definitely an individual!

Do these apply?

Age and Sex

Disease

Environment

- other drugs

Genetic variation