Metabolism

Objectives

- Describe various processes by which drugs are metabolized
- Describe induction and inhibition of metabolism
- Use the venous equilibration model to describe hepatic clearance and the effect of liver disease on drug elimination

Metabolism

- Elimination by transformation of the drug
- Usually results in more polar compound
  - easier urinary excretion - less reabsorption
  - usually inactive - hindered transport, doesn't fit receptor
- Overall effect is removal of the drug effect
- Enzymatic catalysis
  - Liver, intestinal wall, kidney, skin, blood

Metabolic Reactions

- Phase I
  - Oxidation
  - Reduction
  - Hydrolysis
- Phase II
  - Conjugation

Oxidation

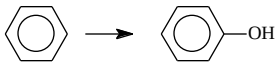
- Phase I
- Addition of oxygen or removal of hydrogen
- Endoplasmic reticulum
- Common Reactions include:
  - Alkyl group -> alcohol
  - Aromatic ring -> phenol
  - Oxidation at S or N
  - Oxidative dealkylation
  - Monoamineoxidase
  - Alcohol dehydrogenase

Alkyl Group > Alcohol

- e.g. phenobarbitone

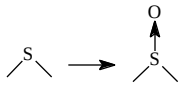
Aromatic Ring > Phenol

- e.g. phenytoin



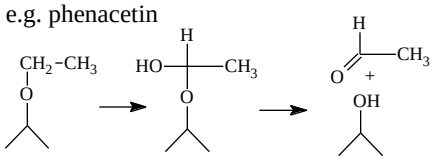
Oxidation at S or N

- e.g. chlorpromazine



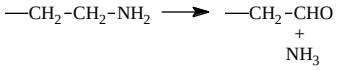
Oxidative Dealkylation

- e.g. phenacetin



Monoamine oxidase

- e.g. 5-hydroxytryptamine



Alcohol Dehydrogenase

Reduction

Phase I

- Addition of a hydrogen or removal of oxygen
- azo (-N=N-) or nitro group ($-NO_2$) --> amine ($-NH_2$)

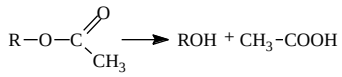
Hydrolysis

Phase I

- Addition of water
- In blood (esterases) and liver

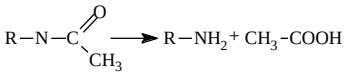
Ester -> Alcohol and Acid

- e.g. aspirin to salicylic acid



Amide -> Amine and Acid

- e.g. procainamide



Conjugation

Phase II

- Addition of a molecule in the body
- May be preceded by a Phase I process
- Glucuronidation
  - In the liver
  - Aliphatic alcohols and phenols
  - e.g. bilirubin, thyroxine, hydroxylated morphine

Conjugation…

- Acylation
  - Especially acetylation
  - e.g. sulfonamide
- Glycine addition
  - e.g. nicotinic acid
- Sulfation
  - e.g. morphine, paracetamol (acetaminophen)

Metabolism

- More polar compounds
  - e.g. C-H -> C-OH
  - e.g. addition of acetyl or sulfate group
- Generally more water soluble and faster urinary elimination

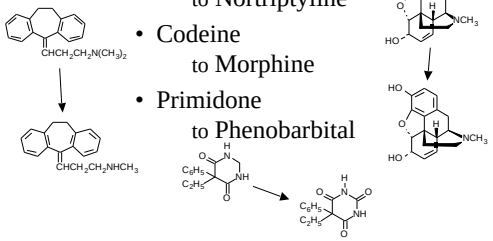
Insoluble Metabolites

- Metabolites can be less water soluble
- e.g. Acetyl metabolites of some sulfonamides
  - Resulted in crystalluria after precipitation in tubules
  - Remember all that water reabsorption
- Triple sulfas
- Development of sulfonamides with soluble metabolites

Active Metabolites

or Pro-Drugs ?

- Amitriptyline
  to Nortriptyline
- Codeine
  to Morphine
- Primidone
  to Phenobarbital



Induction of Metabolism

Increase in Enzyme Activity

- Phenobarbitone induces it's own metabolism and that of other drugs
  - phenytoin, warfarin
- Carbamazepine induces it's own metabolism - over 4-5 days
  - $t_{1/2}$ from 36 to 21 hr
- Cigarette smoking induces drug metabolism
  - e.g. theophylline $t_{1/2}$ 4 hr vs. 7 hr

Inhibition of Drug Metabolism

competitive inhibition

- Examples
  - warfarin inhibits tolbutamide, phenytoin
  - phenylbutazine inhibits warfarin
  - cimetidine inhibits warfarin
- Dose adjustment necessary

Systemic Clearance

with First Order Kinetics

- single dose

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

- multiple dose (at Steady State)

$$CL = \frac{k0}{Cp^{ss}} = \frac{F \cdot Dose}{\overline{Cp} \cdot \tau}$$

Venous Equilibration Model

for organ (liver) clearance

Venous Equilibration Model…

- Measuring drug concentration entering and leaving liver

$$\text{Organ Clearance} = \frac{Q_L \cdot (Ca - Cv)}{Ca} = Q_L \cdot E$$

- where Q_L is liver blood flow and E is the extraction ratio

Extraction Ratio

Values from 0 to 1

- Fraction Removed by Liver in one Pass
- High Value of E means
  - high clearance by the liver
  - very little unmetabolized gets through unchanged
- Low Value of E means
  - little metabolism
- CL_L and E measures of extent of metabolism

Parameters of the Model

- Total hepatic blood flow, Q
- Fraction unbound, fu
- Free intrinsic clearance, CL_{int}
  - clearance from liver plasma water
  - no flow or binding constraints
  - saturable since enzyme mediated

The Mathematical Model

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

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

$$CL = Q \cdot E$$

- Can consider effect of each parameter on overall hepatic clearance

Flow Limited Drugs

high $fu \cdot CL_{int}$ value

$$\text{High } fu \cdot CL_{int} \left(= CL_{int}^{total}\right)$$

$$fu \cdot CL_{int} >> Q$$

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

- thus CL is flow limited (equal to Q)
- independent of changes in fu or CL_{int}
- e.g. lidocaine, propranolol, morphine

Capacity Limited Drugs

low $fu \cdot CL_{int}$ value

$$\text{Low } fu \cdot CL_{int} \left(= CL_{int}^{total}\right)$$

$$fu \cdot CL_{int} << Q$$

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

- thus CL is determined by intrinsic clearance
- independent of changes in Q
- e.g. phenytoin, warfarin, quinidine

Other Drugs

$fu \cdot CL_{int} \approx Q$

- capacity limited - binding insensitive
- all three parameters important
- e.g. theophylline, antipyrine

Systemic Availability

- Once the drug is absorbed across the GI tract membrane the drug must get through the liver
- The extent of the first-pass metabolism can be determined from the extraction ratio, E
- Fmax = 1 - E
- e.g. morphine P.O.. 30 mg cf. IV 5 mg

Liver Disease

Systemic Availability

- A small change in E may have a large effect on F
  - e.g. E = 0.95 to 0.90 causes F to double
- In chronic liver disease porta-systemic shunt may reduce First-Pass effect
  - High clearance drugs may be well absorbed after P.O. dosage
  - e.g. morphine 30 mg P.O. may be similar to 30 mg I.V.

Objectives

- Describe various processes by which drugs are metabolized
- Describe induction and inhibition of metabolism
- Use the venous equilibration model to describe hepatic clearance and the effect of liver disease on drug elimination