Chapter 28

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
  – Monoamine oxidase
  – Alcohol dehydrogenase

Alkyl Group > Alcohol

• e.g. phenobarbitone

\[
\text{CH}_2\text{CH}_3 \rightarrow \text{CH} = \text{CH}_3
\]
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

\[
\text{CH}_2\text{-CH}_2\text{-NH}_2 \rightarrow \text{CH}_2\text{-CHO} + \text{NH}_3
\]

Alcohol Dehydrogenase

\[
\text{CH}_2\text{-CH}_2\text{-OH} \rightarrow \text{CH}_2\text{-CHO}
\]

Reduction
Phase I
• Addition of a hydrogen or removal of oxygen
• azo (-N=N-) or nitro group (-NO₂) --> amine (-NH₂)
Hydrolysis

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

Ester $\rightarrow$ Alcohol and Acid
- e.g. aspirin to salicylic acid
  \[
  R\text{--O--C--O} \overset{\text{CH}_3}{\rightarrow} \text{ROH} + \text{CH}_3\text{--COOH}
  \]

Amide $\rightarrow$ Amine and Acid
- e.g. procainamide
  \[
  R\text{--N--C--O} \overset{\text{CH}_3}{\rightarrow} R\text{--NH}_2 + \text{CH}_3\text{--COOH}
  \]
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 its own metabolism and that of other drugs
  - phenytoin, warfarin
- Carbamazepine induces its 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
  – phenylbutazone inhibits warfarin
  – cimetidine inhibits warfarin
• Dose adjustment necessary

Systemic Clearance

with First Order Kinetics

• single dose
  \[ CL = \frac{F \cdot \text{Dose}}{\text{AUC}} = \frac{0.693 \cdot V_{\text{area}}}{t_{1/2}} \]

• multiple dose (at Steady State)
  \[ CL = \frac{k_0}{C_p^{\infty}} \cdot \frac{F \cdot \text{Dose}}{C_p \cdot \tau} \]

Venous Equilibration Model

for organ (liver) clearance
Venous Equilibration Model...

- Measuring drug concentration entering and leaving liver

\[
\text{Organ Clearance} = \frac{Q_L \cdot (C_a - C_v)}{C_a} = Q_L \cdot E
\]

- 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

\[ \text{CL} = Q \cdot \frac{\text{fu} \cdot \text{CL}_{\text{int}}}{(Q + \text{fu} \cdot \text{CL}_{\text{int}})} = \frac{Q \cdot \text{CL}_{\text{int}}^{\text{total}}}{Q + \text{CL}_{\text{int}}^{\text{total}}} \]

with

\[ E = \frac{\text{fu} \cdot \text{CL}_{\text{int}}}{Q + \text{fu} \cdot \text{CL}_{\text{int}}} \]

\[ \text{CL} = Q \cdot E \]

- Can consider effect of each parameter on overall hepatic clearance

Flow Limited Drugs

- high \( \text{fu} \cdot \text{CL}_{\text{int}} \) value
  - High \( \text{fu} \cdot \text{CL}_{\text{int}} \) (\( \approx \text{CL}_{\text{int}}^{\text{total}} \))
  - \( \text{fu} \cdot \text{CL}_{\text{int}} \) >> \( Q \)
  - \( \text{CL} = Q \cdot \frac{\text{fu} \cdot \text{CL}_{\text{int}}}{\text{fu} \cdot \text{CL}_{\text{int}}} = Q \)
  - thus \( \text{CL} \) is flow limited (equal to \( Q \))
  - independent of changes in \( \text{fu} \) or \( \text{CL}_{\text{int}} \)
  - e.g. lidocaine, propranolol, morphine

Capacity Limited Drugs

- low \( \text{fu} \cdot \text{CL}_{\text{int}} \) value
  - Low \( \text{fu} \cdot \text{CL}_{\text{int}} \) (\( \approx \text{CL}_{\text{int}}^{\text{total}} \))
  - \( \text{fu} \cdot \text{CL}_{\text{int}} \ll Q \)
  - \( \text{CL} = Q \cdot \frac{\text{fu} \cdot \text{CL}_{\text{int}}}{Q} = \frac{\text{fu} \cdot \text{CL}_{\text{int}}}{Q} = \text{CL}_{\text{int}}^{\text{total}} \)
  - thus \( \text{CL} \) is determined by intrinsic clearance
  - independent of changes in \( Q \)
  - e.g. phenytoin, warfarin, quinidine
Other Drugs

\( \text{fu} \cdot \text{CL}_{\text{int}} = Q \)

- 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, \( E \)
- \( F_{\text{max}} = 1 - E \)
- 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.
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