DRUG ELIMINATION II

BILIARY EXCRETION
MAMMARY, SALIVARY AND PULMONARY EXCRETION
ROUTE OF DRUG ADMINISTRATION AND EXTRAHEPATIC DRUG METABOLISM

• The decline in plasma concentration after drug administration results from drug elimination or removal by the body (metabolism/biotransformation and renal excretion)

• The main site of metabolism is liver, others are those tissues associated with portals of drug entry into the body include: lung, skin, GI mucosal cells, microbiological flora in the distal portion of the ileum, and large intestine. Also the kidney may be involved

• Knowledge of the fraction of the drug that is eliminated by metabolism and the fraction of drug that is eliminated by excretion is important to predict whether a change in drug elimination is affected by renal disease, hepatic disease, or drug-drug interaction
Hepatic Clearance

- Hepatic clearance defined as the volume of blood that perfuses the liver and is cleared of drug per unit time

\[
Cl_T = Cl_{NR} + Cl_R
\]

\[
Cl_H = Cl_T - Cl_R
\]

- **Extrahepatic metabolism**: some drugs are metabolized extensively outside the liver. To access extrahepatic metabolism is to calculate hepatic (metabolic) clearance
Example 1

- Morphin clearance, \( \text{Cl}_T \), 75 kg patient is 1800 mL/min. After oral dose, 4% is excreted unchanged in the urine (\( \text{fe}=0.04 \)). The fraction of drug absorbed after oral dose is 24% (\( F=0.24 \)). Hepatic blood flow=1500 ml. Does morphine have any extrahepatic metabolism?
- \( \text{Fe}=0.04 \), \( \text{Cl}_R=0.04 \text{ Cl}_T \), \( \text{ClNR}=0.96\text{Cl}_T=0.96 \times 1800 \text{ mL/min}=1728 \text{ mL/min} \). Hepatic blood flow=1500 mL/min, so the drug appears to be metabolized faster than the hepatic blood flow – thus some are metabolized outside the liver.
- The low fraction of drug absorbed after an oral dose indicates that much of drug are metabolized before reaching the systemic circulation.
Example 2

- Flutamide, for prostate cancer, is rapidly metabolized to an active metabolite, $\alpha$-hydroxyflutamide in human. $CSS = 51 \text{ ng/ml}$ after oral multiple dose of 250 mg 3x8 jam per day. Calculate the $Cl_T$ and $Cl_H$ assuming that flutamide is 90% metabolized and 100% absorbed

- Clue: $Cl_T = \frac{FD0}{Cav\infty \tau}$
Biliary Excretion

- Biliary system of the liver is important for excretion of bile and excretion of drugs
- Anatomically, the intra hepatic bile ducts join outside the liver to form the common hepatic duct. The bile that enters the gall bladder becomes highly concentrated
- The hepatic duct, containing hepatic bile, join the cystic duct that drains the gallbladders to form the common bile duct which then empties into the duodenum
- Bile consists primarily of water, bile salts, bile pigments, electrolytes, and cholesterol and fatty acids
- The hepatic cells that lining the bile canaliculi are responsible for the production of bile. The production of biles is an active secretion process. Separate active biliary secretion processes are for organic anions, cations, and for polar, uncharged molecules
• Drugs that are excreted mainly in the bile have molecular weights >500. Drugs with MW between 300-500 are excreted both in urine and in bile – decrease in one excretory route results in a compensatory increase in excretion via the other route. Compounds with MW <300 are excreted via kidneys into urine.

• Relatively high MW drugs excreted into bile usually require a strongly polar groups, they are mostly metabolites, very often glucuronide conjugates, and most are more polar than the parent drug.

• The formation of a glucuronide increases the MW by nearly 200, as well as increasing the polarity.

• Drugs excreted into bile: digitalis glycosides, bile salts, cholesterol, steroids, and indomethacin.

• Compounds that enhance bile production stimulate the biliary excretion of drugs normally eliminated by this route.

• Phenobarbital: induces mixed-function oxidase activities, stimulate the biliary excretion of drugs by 2 mechanisms, increase the formation of glucuronide metabolite and increase in bile flow. Compounds decrease the bile flow or cause cholestatis will decrease biliary excretion. The route of administration: orally or intravenously.
Biliary Clearance

• The rate of drug elimination may be measured by monitoring the amount of drug secreted into the GI perfusate using a special intubation technique that blocks off a segment of the gut with an inflating balloon. In animals, bile duct cannulation allows both the volume of the bile and the concentration of drug in the bile to be measured directly.
• Assuming an average bile flow of 0.5-0.8 mL/min in humans, biliary clearance can be calculated if the bile concentration, \( C_{\text{bile}} \), is known.

\[ Cl_{\text{biliary}} = \frac{\text{bile flow} \times C_{\text{bile}}}{C_P} \]

• Alternatively, using the perfusion technique, the amount of drug eliminated in bile is determined from the GI perfusate, and \( Cl_{\text{biliary}} \) may be calculated without the bile flow rate, as follows

\[ Cl_{\text{biliary}} = \frac{\text{amount of drug secreted from bile per minute}}{C_P} \]

• Drug should be given parentally to avoid any complication of unabsorbed drug in the feces
Enterohepatic Circulation

- A drug/metabolite is secreted into bile – upon contraction of the gallbladder is excreted into the duodenum via common bile duct – excreted into the feces or may be reabsorbed and become systemtically available. This circle is called enterohepatic circulation.

- Drugs – glucuronide conjugate – hydrolyzed in the gut back to the parent drug by β-glucuronidase enzyme present in the intestinal bacteria – the parent drug becomes available for reabsorption.
Significance of Biliary Excretion

- Difficult to determine whether the presence of oral drug in feces comes from biliary excretion or incomplete absorption.
- Parenteral drug in feces – some of the drug was excreted in the bile – secretion in bile is an active process – can be saturated with high drug concentration. Other drugs may compete for the same carrier system.
• Enterohepatic circulation after a single dose is not as important as multiple dose or a very high dose of drug. After reabsorption the large amount of drug – affect the absorption and elimination rate constants, the biliary secretion also can become saturated – altering the plasma level-time curve

• Drug undergo enterohepatic circulation show a small secondary peak in the plasma drug concentration-time curve. The first is for GI absorption, the second emerges as biliary-excreted drug is reabsorbed
Pulmonary, Salivary Excretion

- Lung is a major organ of excretion for gaseous and volatile substance
- Most anaesthetics – extensively eliminated in expired air
- Salivary recycling
- Dependent on pH partition and protein binding
- Good indicating of drug concentration in plasma, small contribution to total elimination