The First Pass Effect

How are most drugs eliminated from the body

1. Metabolism → Liver —
   • chemically changes drug to an inactive form (metabolite
   • enzymes in the liver react with drug
   • drug in blood → metabolite in blood
   • enzymes of metabolism are located in the smooth endoplasmic reticulum of the hepatocyte
     • unbound, lipophilic drugs

2. Excretion → Kidney —
   • unchanged drug is excreted into the kidney
     • filtered or actively secreted and not reabsorbed (or only partially reabsorbed)
     • drug in blood → unchanged drug in urine

Blood Supply to the Kidneys and Liver

- Kidney – renal artery in, renal vein back to inferior vena cava
- Liver – common hepatic artery and portal vein in (dual blood supply), hepatic vein back to inferior vena cava

Drug Elimination

- Kidney – excretes unchanged drug from the systemic circulation
- Liver – metabolizes drug from the portal circulation and the systemic circulation
Metabolism

- Occurs mostly in the liver but may also occur in any mucosal membrane that the drug has to cross to be absorbed into the systemic circulation
  - small intestine
  - rectal
  - nasal
  - vaginal
- The drug has to be susceptible to metabolism by the specific enzymes in the mucosal membrane
  - cytochrome P450 enzymes

First Pass Metabolism

- Metabolism of the drug before it reaches the systemic circulation
  - drug may be absorbed and still not reach the systemic circulation
    - oral = gut wall metabolism and hepatic metabolism can alter amount of drug reaching the systemic circulation
    - Some, all or none of the drug may be metabolized prior to reaching the systemic circulation.
      - none = no first pass effect
    - A constant fraction of the drug dose that is metabolized prior to reaching the systemic circulation
      - 25% \( \rightarrow \) 0.25 (25% of the dose is metabolized prior to reaching the systemic circulation)
      - Patient take 100 mg but only 75 mg reaches the systemic circulation assuming all 100 mg were absorbed.
        - what other factors could prevent a drug from reaching the systemic circulation?

First Pass Effect

- The first pass effect occurs when the drug is metabolized prior to reaching the systemic circulation.
  - gut wall metabolism
  - liver metabolism
Systemic Circulation

First Pass Effect

- Patient swallows the tablet
- Drug from dosage form dissolves in the GIT
- Solution of drug is then available for absorption
- Small intestine is the primary site of drug absorption
- Drug diffuses across the GI epithelium and enters the mesenteric blood supply
- Mesenteric blood supply drains into the hepatic portal vein
- Drug is carried to the liver
• What happens if a solution of drug is injected into a vein in the arm?  
  – leg?  
  – head?  
• What happens if a solution of drug is administered to the eye?  
• What happens if a suspension of drug is administered intramuscularly?  
• What happens if a tablet is taken orally?

Case:  
• Two patients are prescribed 200 mcg Actiq transmucosal lozenges (aka lollipop) for the treatment of break through pain.  
• Patient A places the lozenge in their mouth between their cheek and gum and actively sucks on the lozenge until the feel pain relief.  
• Patient B places the lollipop in their mouth and after a few minutes chews up the lozenge and swallows the dosage form but never finds pain relief.

Case:  
• Patient A has patient B have different pain relief.  
• What is causing the difference in the patients pain relief? They both took the same dose.... right?........  
• Which patient is most likely to have pain relief?
• Fentanyl Sucker (400 mcg)
  – 25% of dose is absorbed through the buccal mucosa (100 mcg)
  • rapid absorption
  – 75% of dose is swallowed and absorbed through GIT (300 mcg)
  • slow absorption
    – 50% of dose is eliminated by first pass effect (200 mcg)
    – 25% of dose reaches the systemic circulation (100 mg)
  – 50% absolute available (200 mcg)
  – Don’t chew and swallow

**Buccal Delivery**

• Between your cheek and gum

**Challenge Question**

• If a drug is a pro-drug, what is the preferred route of administration?