PHARMACOKINETICS: Metabolism/Biotransformation (p.1)

Drugs are eliminated from the body in two major ways:
metabolism/biotransformation by the liver and/or excretion (mostly by the kidneys)

Rich **blood supply** to the liver
- 20% arterial blood directly from heart
- 80% venous blood from GI tract (hepatic-portal vein)
  - "First pass effect"

1. Liver, **liver enzymes**
   microsomal enzymes, **P450** enzymes
   (CYP1A2, CYP2D6, CYP2C9, CYP3A4, CYP2C19, etc.)
   metabolize lipids, steroid hormones, and most drugs
   (see handouts)

2. **Four types of chemical changes**
   a. oxidation

   b. conjugation

   c. reduction

   d. hydrolysis

3. **Inactive metabolites**
   original molecule changed so that it no longer can activate RSs
   most metabolites are inactive

PHARMACOKINETICS: Metabolism/Biotransformation (p.2)

3. **Inactive Metabolites** (cont.)
   usually the molecule becomes less able to pass out of bloodstream or pass through BBB (molecule becomes ionized, less lipid soluble, more water soluble)
   increased chance that molecule will pass into kidney and be excreted in urine

4. **Active metabolites**
   some metabolites are active, can get to & can activate RSs
   may have **same or different effects** as the original molecule
   some original molecules are inactive and only its metabolite is active
   implications for the **drug's duration** of effect

   e.g. codeine – about 10% biotransformed into morphine (more powerful effects vs. codeine)
   Valium (diazepam) --- active metabolite extends duration

5. **Enzyme inhibitors/suppressor**
   e.g. Tagamet (cimetidine)
   implications for repeated dosing, & dose levels
   drug interactions

6. **Enzyme inducers**
   e.g. Tegretol (carbamazepine)
   e.g. ETOH & barbiturates

PHARMACOKINETICS: Metabolism/Biotransformation (p.3)

6. **Enzyme inducers** (cont.)

e.g. **other inducers**: PCBs (polychlorinated biphenyls), many plastics, insecticides, lubricants, heat-exchange fluids used in refrigerators/air conditioners

note: P450 inducers effect on **hormones**, BC pills

note: crucial importance of a **good clinical Hx**

What drugs do you take? Why? When? How long? How much? Do you drink alcohol? Smoke cigarettes? Drink caffeinated beverages? Use OTC products?

note: **wide individual differences** in rates/extent of metabolism (based on variations related to age, sex, race, health, other drug use)

rapid metabolizers vs. **slow metabolizers**…clinical implications

note: try to give pt. drug often enough & at right dosage to keep within the **therapeutic range/index** (where drug is effective but not toxic)

related to issues of pt. **compliance** in taking drug…

1. **on-going monitoring** of pt. is necessary with repeated dosing, a dynamic system…