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

   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…