

# DRUG DRUG INTERACTIONS

## Interaction Mechanisms

- Pharmacokinetic Effects
  - 1. Absorption
    - Drug binding in the GI tract and other tissues (P-glycoprotein)
    - GI motility alterations (poor intestinal transport through the GI tract)
    - GI pH alterations (ionized versus unionized drug ratio)
    - Intestinal flora alterations (microbial metabolism vs. absorption)
    - Drug metabolism alterations within intestinal wall (CYP-450)
  - 2. Protein-Binding Displacement (drug-drug albumin)
  - 3. Modified Renal Excretion (excretion site-acidic drugs)
  - 4. Modified Nonrenal Excretion (enterohepatic recirculation)
  - 5. CYP-450 Enzyme induction (more enzyme produced)
  - 6. CYP-450 Enzyme inhibition (enzymes present inhibited)

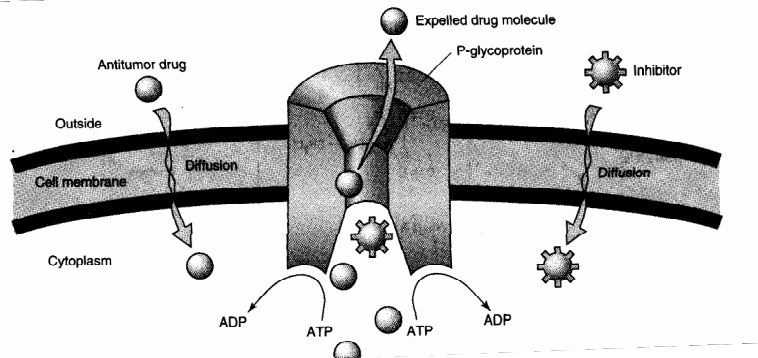
## Interaction Mechanisms

- Pharmacodynamic Effects
  - Antagonistic effects
  - Synergistic Side effects
  - Indirect Pharmacodynamic effects
    - Ex: Anti-histamines are muscarinic receptor antagonists

## Interaction Mechanisms

- Effects of P-glycoproteins
  - P-glycoprotein is a \_\_\_\_\_ protein located in many tissues that "\_\_\_\_\_" an assortment of structurally and mechanistically unrelated compounds
  - The higher the affinity of a drug for P-glycoprotein, \_\_\_\_\_
  - *Chemical and Engineering News* June 5, 2000 pgs. 63-73 "Drug Discovery: Filtering out failures early in the Game"

# P-Glycoprotein



## P-Glycoprotein

- Some drugs induce the overexpression of P-glycoprotein
- Result: \_\_\_\_\_
- Located in many tissues / cells
- Controls uptake and transport of a variety of compounds
- Plays a role in \_\_\_\_\_
  - GI tract, blood-brain barrier, liver biliary hepatocytes and renal proximal tubule cells, testis, adrenal gland and pregnant uterus

# P-Glycoprotein

## Known substrates

- Cyclosporine - Neoral® - Immunosuppressant
- Dexamethasone - Decadron® - Corticosteroid
- Digoxin - Lanoxin® - Chronic Heart Failure
- Diltiazem - Cardizem® - Calcium channel blocker (angina)
- Etoposide - VePesid® - Anti-neoplastic agent
- Hydrocortisone - Cortef® - Corticosteroid
- Nicardipine - Cardene® - Calcium channel blocker (hypertension)
- Paclitaxel - Taxol® - anti-neoplastic agent
- Tacrolimus - Prograf® - Immunosuppressant
- Verapamil - Calan® - Calcium channel blocker/hypertension/angina
- Vinblastine - Velban® - anti-neoplastic agent
- Vincristine - Oncovin® - anti-neoplastic agent

# Cytochrome P450

## Inducers and Inhibitors:

- Primary method to eliminate drugs
- CYP mainly in the liver; also GI epithelium and other tissues
- Pharmacogenetic factors → \_\_\_\_\_

## Cytochrome P450

- At LEAST 50 isoenzymes, grouped based on their a.a. sequences
- Example: CYP3A4: Cytochrome P450, family "\_\_\_", subfamily "\_\_\_" and the \_\_\_ enzyme in the subfamily
- Most CYP-450 enzymes involved in drug metabolism belong to the three distinct families, \_\_\_\_\_

## Cytochrome P450

### Enzyme induction:

- An adaptive process by which the body perceives the \_\_\_\_\_ of a lipid-soluble compound (a drug) that needs to be eliminated from the body
- This leads to a stimulation of the isoenzyme synthesis \_\_\_\_\_ its amounts
- Slow to disappear, must wait for enzyme life-time turnover

## Cytochrome P450

### Inhibition:

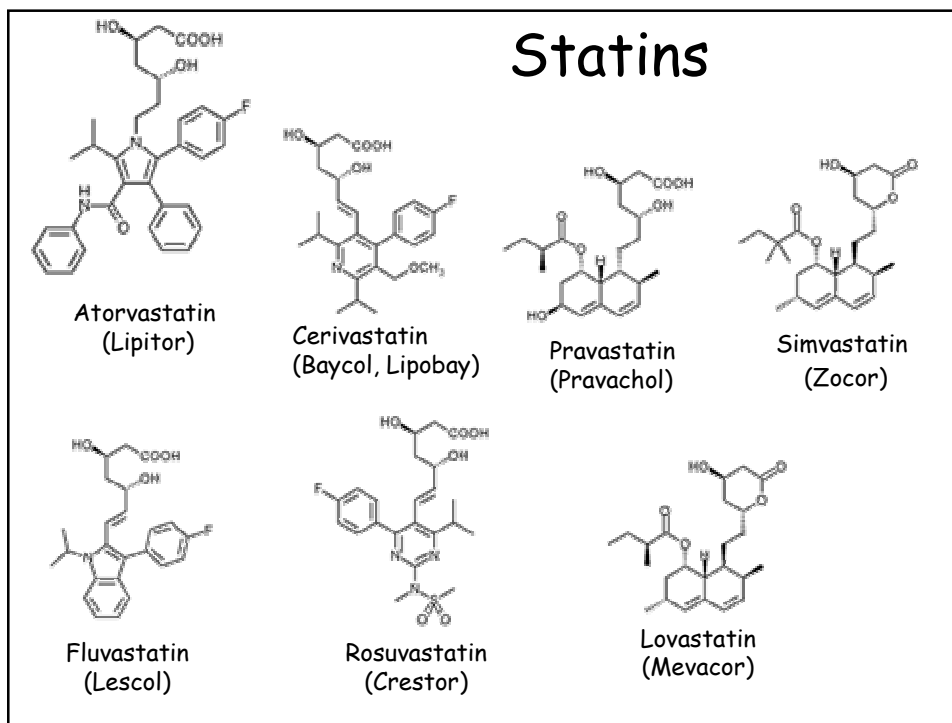
- Enzyme inhibition occurs \_\_\_\_\_ than induction
- So, inhibition the most clinically relevant DI's.
- Occurs when sufficient concentration of the inhibitor is present in the blood stream.
- Adverse effects manifest themselves after sufficient accumulation of the offending agent reaches a new steady-state serum concentration or toxic level.
- Two types of inhibition possible:
  - Competitive inhibitor -
  - Non-competitive inhibitor -

## Grapefruit Juice

- Inhibits P-glycoprotein and CYP3A4 (up to 24 hours) present in the GI tract gut wall
- \_\_\_\_\_ blood concentration of drugs given orally that are metabolized by CYP3A4
- \_\_\_\_\_ on IV administered drugs metabolized by CYP3A4
- This DI is very important in drugs that are normally subject to \_\_\_\_\_  
\_\_\_\_\_
- Best advice for patients: NO grapefruit juice.

# Statin Drug Interactions

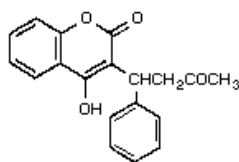
- Key: metabolic differences
  - Atorvastatin, simvastatin and lovastatin undergo CYP3A4 conversion
  - Fluvastatin is metabolized by CYP2C9
  - Pravastatin is metabolized via sulfation and processed by P-glycoprotein
  - Cerivastatin is metabolized primarily by CYP2C8 and to a much lesser extent by CYP3A4



## Statin Drug Interactions

- **Cyclosporine** –A CYP3A4 substrate
  - Increase lovastatin levels, myopathy, rhabdomyolysis
  - No interaction with *Pravastatin* and *Fluvastatin*
- **Erythromycin**
  - An inhibitor of CYP3A4
  - Leads to increased levels of statins
  - Other macrolides such as azithromycin or dirithromycin are alternative drugs since they DO NOT inhibit CYP3A4
  - Clarithromycin and troleandomycin are also inhibitors of CYP3A4
- **Azole antifungals (Itraconazole, ketoconazole, fluconazole)**
  - Potent inhibitor of CYP3A4
  - Fluconazole inhibits CYP2C9 - do not use Fluvastatin
  - Possible therapeutic alternative (if correct indication) is terbinafine - Lamisil®

## Warfarin Interactions

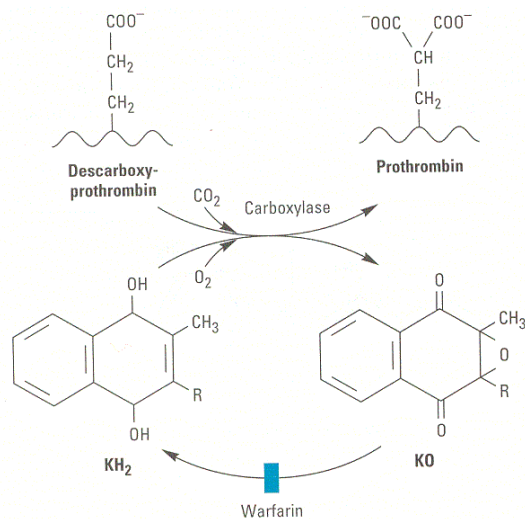


- Warfarin: racemic mixture of R- and S- stereoisomers
  - Due to two stereoisomers, pharmacist should view warfarin as two different anticoagulant drugs
  - S-Warfarin is \_\_\_ more potent than R-Warfarin
  - S-Warfarin is metabolized by \_\_\_\_\_
  - R-Warfarin is metabolized by \_\_\_\_\_ and \_\_\_\_\_

# Warfarin Interactions

- Mechanism: Alteration of intestinal absorption and clearance
- Inhibition of S-warfarin clearance
  - Trimethoprim / sulfamethoxazole - Bactrim<sup>®</sup>, Septra<sup>®</sup> - *antimicrobial*
  - Metronidazole - Flagyl<sup>®</sup> - *treat amebiasis (infection)*
  - Amiodarone - Cordarone<sup>®</sup> - *ventricular arrhythmias*
- Inhibition of R-warfarin clearance
  - Cimetidine - Tagamet<sup>®</sup> - *Ulcers & GERD*
  - Omeprazole - Prilosec<sup>®</sup> - *proton pump inhibitor*
  - Amiodarone - Cordarone<sup>®</sup>
- Induction of warfarin metabolism →

# Warfarin Interactions



## Warfarin Interactions

- Decreased synthesis of normal clotting factors increases anti-coagulation effect of warfarin
  - Fluctuation in dietary Vitamin K content
    - Increased Vit. K leads to \_\_\_\_\_ in anti-coagulant effect
  - Hepatic disease or dysfunction

## St. John's Wort (Herbal)

- Is associated with a 50% reduction in the effectiveness of the CYP 3A4 enzyme subsystem
- May induce P-glycoprotein
- Cyclosporine -
- Digoxin -
- Oral contraceptives -
- Protease inhibitors -
- SSRI's -
- Theophylline -
- Anticoagulants -