Drug Interactions

Scott R. Penzak, Pharm.D.
Pharmacokineticist
Clinical Pharmacokinetics Research Laboratory
Clinical Center Pharmacy Department
National Institutes of Health

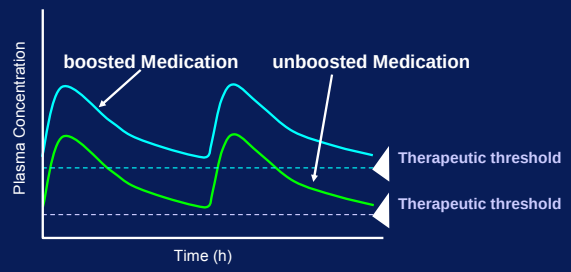
Drug Interactions

- ***Drug Interaction:***
  - *The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone*
  - May be harmful: toxicity, reduced efficacy
  - May be beneficial: synergistic combinations, pharmacokinetic boosting, increased convenience, reduced toxicity, cost reduction

Beneficial Drug Interactions

- **Saquinavir & ritonavir**
  - Saquinavir poorly absorbed, TID dosing, high pill burden (18 caps per day!)
  - Combination with ritonavir results in 20-fold increase in Cpss
  - Allows for BID dosing and decreased dose from 1200 mg TID to 1000 mg BID (1600 QD dosing is also possible)
- **Indinavir, amprenavir, atazanavir + ritonavir**
- **Cyclosporin and ketoconazole**
  - Difficult to determine doses due to large interpatient variability in CYP3A (and P-gp) activity

PK Interactions between PIs: Pharmacoenhancement



Slide Courtesy of Dr. David Back. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002.

Beneficial Drug Interactions: RTV + SQV

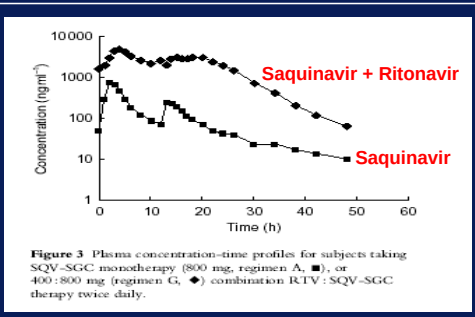


Figure 3 Plasma concentration-time profiles for subjects taking SQV-SGC monotherapy (800 mg, regimen A, ■), or 400:800 mg (regimen G, ◆) combination RTV:SQV-SGC therapy twice daily.

Buss N et al. Br J Clin Pharmacol. 2001 Sep;52(3):255-64.

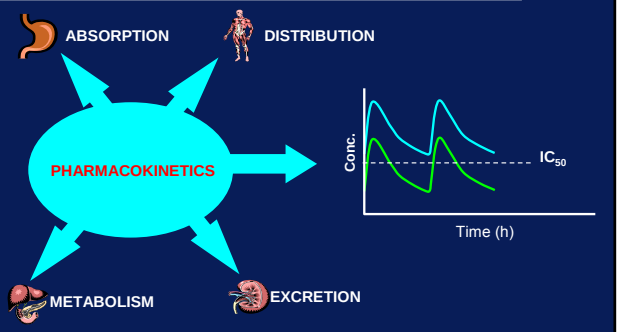
Epidemiology of Drug-Drug Interactions

- **True incidence difficult to determine**
  - Data for drug-related hospital admissions do not separate out drug interactions, focus on ADRs
- **Most data are in the form of case reports**
  - Missing or incomplete information
- **Patients receiving polypharmacy are at risk**
  - 77% of HIV patients on protease inhibitors experience drug interactions
- **Difficulty in assessing role of OTC and herbal drugs in drug interactions**
  - Questions regarding “active” ingredient in herbal meds

Types of Drug Interactions

- **Pharmacodynamic**
  - Related to the drug's effects in the body
  - One drug modulates the pharmacologic effect of another: additive, synergistic, or antagonistic
- **Pharmacokinetic**
  - What the body does with the drug
  - One drug alters the concentration of another
  - *Usually* mediated by cytochrome P450 (CYP)

Pharmacokinetic Interactions



Drug Interactions

Absorption: food, chelation, G.I. motility, pH

Distribution: transport, protein binding

Metabolism: Phase I (CYP450), Phase II (conjugation)

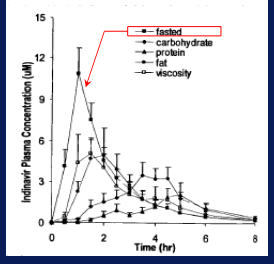
Elimination: Renal (glomerular filtration); transport

Alterations in Absorption

- **Administration with food**
  - Decreased rate of absorption; not extent (↔ AUC):
    - √ Common for many drugs; take without regard to meals
  - Decreased extent of absorption (↓ AUC):
    - √ Indinavir AUC decreased by 77% with high calorie meal; take on an empty stomach
  - Increased extent of absorption (↑ AUC):
    - √ Itraconazole (capsules) AUC increased by 66% with standard meal

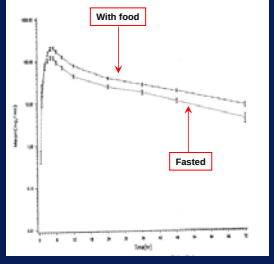
Alterations in Absorption: Food Effects

Indinavir +/- food



Pharm Res. 1999 May;16(5):718-24.

Itraconazole caps +/- food

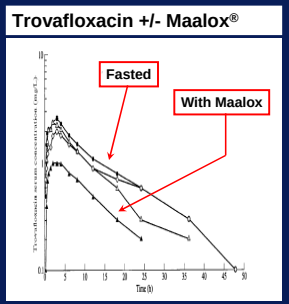


Antimicrob Agents Chemother. 1993 Apr;37(4):778-84.

Alterations in Absorption: Chelation

- **Chelation**
  - Irreversible binding of drugs in the GI tract
  - Tetracyclines, quinolone antibiotics - ferrous sulfate (Fe^{+2}), antacids (Al^{+3}, Ca^{+2}, Mg^{+2}), dairy products (Ca^{+2})
  - Usually separating administration of chelating drugs by 2+ hours decreases interaction effect

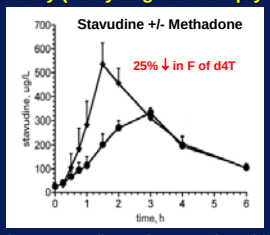
Trovafloxacin +/- Maalox®



J Antimicrob Chemother. 1997 Jun;39 Suppl B:93-7.

Alterations in Absorption: GI Motility

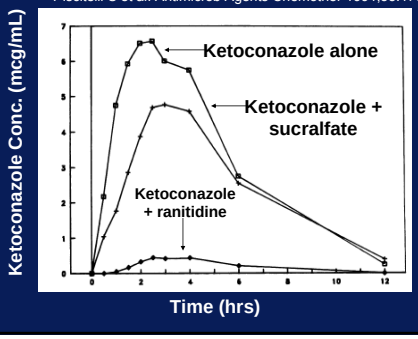
- ↑ GI motility: cisapride, metoclopramide
- ↓ motility: narcotics, antidiarrheals, high calorie meal / viscosity (delayed gastric emptying)



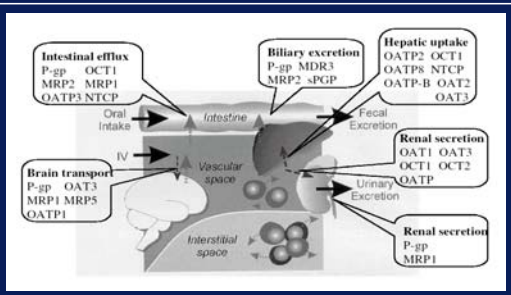
J Acquir Immune Defic Syndr. 2000 Jul 1;24(3):241-8.

Alterations in Absorption

Piscitelli S et al. Antimicrob Agents Chemother 1991;35:1765-1771



Drug Interactions: Transport Proteins

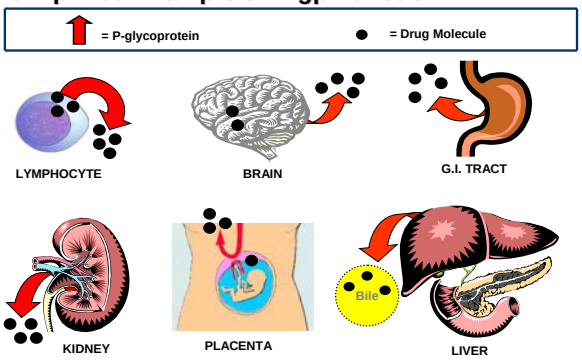


Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica. 2001;31:469-97.

Alterations in Absorption: Drug Transport

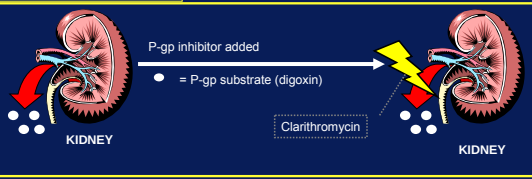
- **Efflux proteins**
  - P-glycoprotein, MRP1, MRP2, OAT3
  - Extrude drug from gut back into lumen limiting drug absorption
  - Transporter induction may result in ↓ absorption
  - Transporter inhibition may result in ↑ absorption
  - Effects often difficult to assess (vs. metabolism; vs. anatomic site)
  - Inhibition may be of clinical significance for drugs that are large molecules, have low bioavailability, dissolve slowly and/or incompletely (clinical significance may be overstated in medical literature)

Simplified Example of P-gp Function



Drug Interactions: Transport Proteins

CONCEPT USING THE KIDNEY



CLINICAL APPLICATION: HEALTHY HUMAN VOLUNTEERS

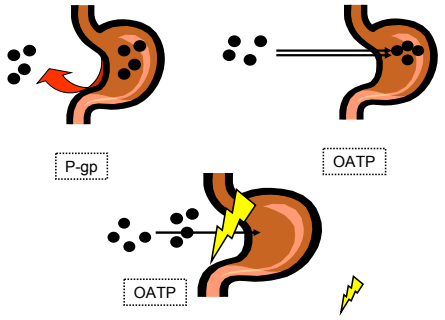
	Digoxin + Placebo	Digoxin + Clarithromycin	*P*
AUC 0-24 hr	14	23	< .05
Cl_R (mL/min)	57	34	< .05

Rengelshausen et al. Brit J Clin Pharmacol 2003;56:32-8.

Alterations in Absorption: Drug Transport

- **Uptake proteins**
  - OATP: located on the luminal border of enterocytes
  - Transport drug across lumen and promote absorption
  - Transporter inhibition may result in ↓ absorption and reduced bioavailability
  - OATP substrates
    - √ Pravastatin, digoxin, fexofenadine, benzylpenicillin
  - OATP inhibitors
    - √ Fruit juices, ritonavir, saquinavir, lovastatin, others?
  - In the intestine, OATP functions *OPPOSITE* of P-gp (i.e. P-gp inhibition *INCREASES* drug absorption while OATP *DECREASES* drug absorption for compounds that are substrates of both proteins

OATP Function: INTESTINE



Alterations in Absorption: Drug Transport

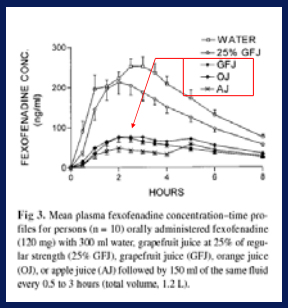


Fig 3. Mean plasma fexofenadine concentration–time profiles for persons (n = 10) orally administered fexofenadine (120 mg) with 300 ml water, grapefruit juice at 25% of regular strength (25% GFJ), grapefruit juice (GFJ), orange juice (OJ), or apple juice (AJ) followed by 150 ml of the same fluid every 0.5 to 3 hours (total volume, 1.2 L).

Clin Pharmacol Ther. 2002 Jan;71(1):11-20.

Alterations in Absorption: anion exchange resins and Gut Flora Modulation

- **Anion exchange resins (i.e. cholestyramine)**
  - Form insoluble complexes with various drugs reducing their absorption
    - √ Warfarin, digoxin, β-blockers, NSAIDS, others?
  - Stagger dose of exchange resin with other meds
    - √ Difficult due to multiple daily dosing of cholestyramine
- **Inhibition of drug-metabolizing enteric bacteria**
  - Antibiotics
    - √ Digoxin (*Eubacterium lentum)*
    - √ Oral contraceptives (bacteria hydrolyze steroid conjugates)
      - – Reports of unplanned pregnancy: causal relationship with antimicrobial administration is controversial

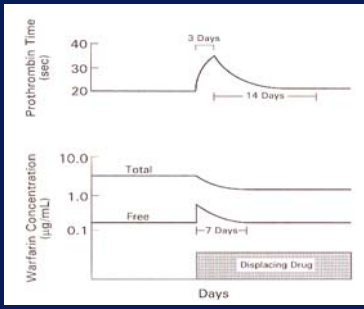
Distribution: Protein Binding Interactions

- **Non-restrictively cleared drugs**
  - Eliminating organ removing most of the drug being presented to it, including the fraction bound to plasma proteins
  - Increase in fu will not lead to a proportional increase in CL
  - No examples of clinically significant protein binding interactions have been identified with non-restrictively cleared drugs

Distribution: Protein Binding Interactions

- **Restrictively cleared drugs**
  - Small fraction of drug extracted during single passage through the eliminating organ ($E \leq f_{ub}$)
  - *Only unbound drug in plasma can be cleared*
  - Increase in f_u leads to proportional increase in total drug CL and decrease in total drug Cpss
  - $Cpss_{ub}$ will return to pre-displacement value after transient increase
    - √ Only likely to clinically significant for drugs with LONG T ½, SMALL Vd, narrow therapeutic range, ↑ PPB
    - √ Example: warfarin displacement from serum albumin by a metabolite of chloral hydrate (trichloroacetic acid)

Distribution: Protein Binding Interactions



- Warfarin + Tri-CA
- F_{ub} : ↑
- C_{ub} : transient ↑ (then ↔)
- Total CL: ↑
- C_{total} : ↓
- C_{bound} : ↓

Principles of Clinical Pharmacology, pg 64

Alterations in Distribution: Protein Binding

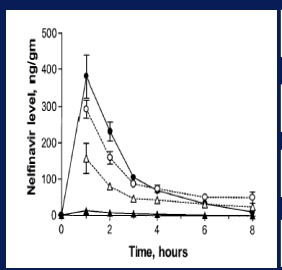
"…the overall clinical importance of plasma protein binding displacement interactions continues to be overstated…"

"Despite the theoretical and experimental data to the contrary, the concept that plasma protein binding displacement is a common cause of clinically significant interactions may still be widely taught in some medical schools, often appears in textbooks and is accepted by many in the medical community and by drug regulators."

Sansom LN & Evans AM. Drug Safety 1995;12:227-233.
Rolan PE. Br J Clin Pharmacol 1994;37:125-128.

Distribution: Drug Transport (P-gp)

^{14}C Nelfinavir +/- LY-335979 in *MDR1a* wild type Mice



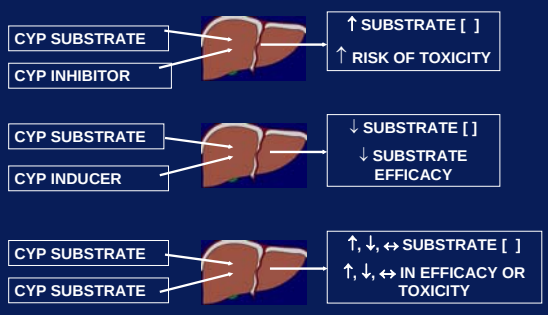
- ● Tissue ^{14}C NFV conc. in brain
  ^{14}C NFV + LY-335979 (P-gp inhibitor)
- O Plasma ^{14}C NFV concentration
  ^{14}C NFV + LY-335979 (P-gp inhibitor)
- Δ Plasma ^{14}C NFV concentration
  ^{14}C NFV + vehicle
- ▲ Tissue ^{14}C NFV conc. in brain
  ^{14}C NFV + vehicle

Choo EF et al. Drug Metab Disposit 2000;28:655-660.

Drug Metabolism Interactions

- **Drug metabolism**
  - Chemical modification of a xenobiotic
  - Phase I (functionalization RX)
    - √ Cytochrome P450 (CYP): i.e. CYP3A4, CYP2D6, CYP1A2 etc.
  - Phase II (synthetic RX)
    - √ Conjugation: i.e. glucuronidation (UGT1A1 etc.)
  - Purpose: detoxification of foreign compounds
  - Anatomic sites: Liver*, Gut*, kidney, lung, brain etc.

Drug Metabolism Interactions



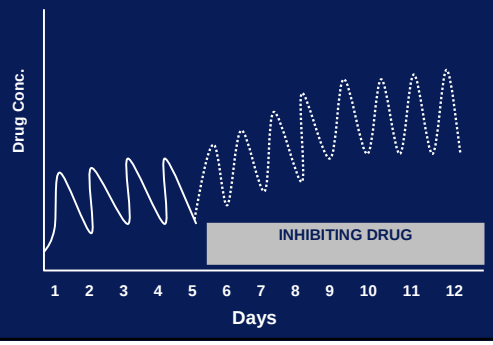
CYP 450 Substrates

- **Drugs may be metabolized by a single isoenzyme**
  - Desipramine/CYP2D6; indinavir/3A4; midazolam/3A, caffeine/CYP1A2; omeprazole/CYP2C19
- **Drugs may be metabolized by multiple isoenzymes**
  - Most drugs metabolized by more than one isozyme
    - √ Imipramine: CYP2D6, CYP1A2, CYP3A4, CYP2C19
  - If co-administered with CYP450 inhibitor, some isozymes may "pick up slack" for inhibited isozyme
- **Extensive listing + references:**
  - http://medicine.iupui.edu/flockhart/table.htm

CYP 450 Enzyme Inhibition

- Usually by competitive binding to enzyme site
- Onset and offset dependent on the half-life and time to steady-state of the inhibitor
  - Fluoxetine & CYP2D6; ritonavir and CYP3A4
- Time to maximum interaction effect dependent on time required for substrate drug to reach new steady-state
- Mechanism-based enzyme inactivation
  - Grapefruit juice and intestinal CYP3A content

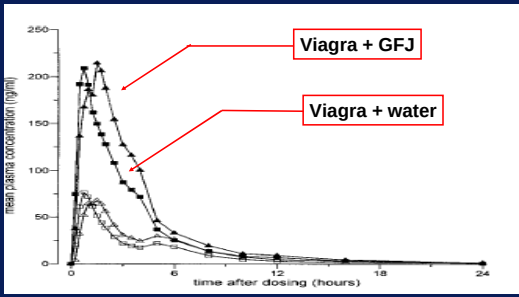
Enzyme Inhibition



CYP 450 Inhibitors

- The "usual suspects"
  - Cimetidine (various)
  - Erythromycin, clarithromycin (3A4)
  - Ketoconazole, itraconazole (3A4)
  - HIV protease inhibitors (esp. ritonavir)
  - Fluoxetine, paroxetine (CYP2D6)
  - Nefazodone (CYP3A4)
  - Grapefruit Juice (intestinal CYP3A4 only)
- Extensive listing with references:
  - http://medicine.iupui.edu/flockhart/table.htm

Sildenafil (Viagra®) + Grapefruit Juice



Jeter A et al. Clin Pharmacol Ther. 2002 Jan;71(1):21-9.

CYP450 Inhibition

- **Key questions:**
  - ✓**What is the toxic potential and therapeutic index of the substrate**
    - ➢ **Terfenadine or digoxin vs sertraline**
  - ✓**What are the other pathways involved in the metabolism of the substrate**
    - ➢ **Zolpidem vs triazolam**
  - ✓**Does the substrate have active metabolites?**
    - ➢ **Codeine → morphine**

CYP450 Induction

- **The "usual suspects"**
  - **Rifampin**
  - **Rifabutin**
  - **Carbamazepine**
  - **Phenobarbital**
  - **Phenytoin**
  - **Nevirapine, efavirenz**
  - **St. John's wort**
  - **Troglitazone, pioglitazone**

http://medicine.iupui.edu/flockhart/table.htm

CYP450 Induction

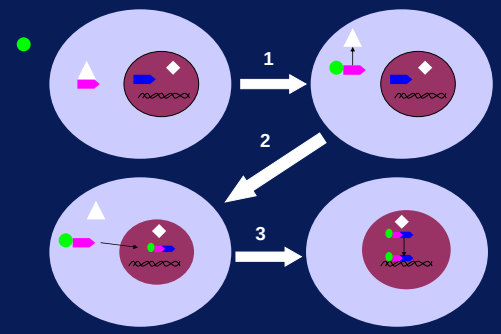
- **Gradual onset and offset**
  - (involves increased DNA transcription and synthesis of new CYP enzymes
- **Onset and offset**
  - Depends on T ½ of inducer, time to make new CYP proteins, and rate of degradation of CYP proteins
- **Results in reduction of plasma concentration of substrate drugs**
  - Risk of therapeutic failure
  - Removal of inducer may lead to toxic concentrations of substrate
  - Induction may lead to formation of toxic metabolite

Regulation of Drug Metabolism and Transport

- **Nuclear Receptors (NR)**
  - Largest known family of transcription factors
  - Function as modulators of gene expression
  - Ligand (drug, bile acid, hormone etc.) binds to vacant NR in the cytoplasm → enters the nucleus & forms homo or heterodimers which complexes to promotor/enhancer regions of target genes
    - √ Simply put: the gene is "switched on" (or off) causing it to produce (or not produce) mRNA and subsequent proteins

Nuclear receptor activation

Adapted from Urquhart et al J Clin Pharm 2007;47:566-78

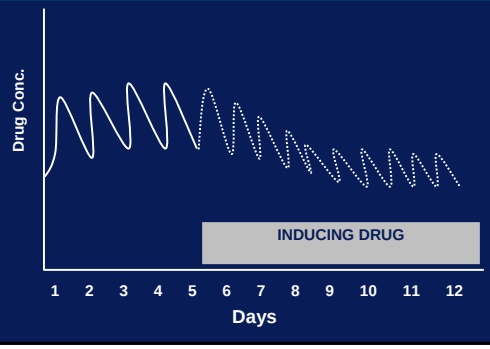


Summary of Nuclear Receptor Activators

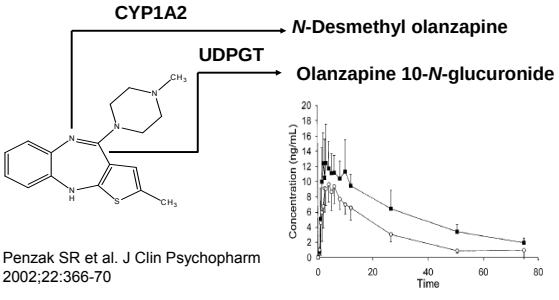
Target Gene	Nuclear Receptor	Ligands
CYP3A4	PXR, CAR, GR, HNF4α, VDR, FXR	PXR: rifampin, dexamethasone + others
CYP2C9	PXR, CAR, GR	CAR: phenobarbital
CYP2C19	CAR, GR	GR: dexamethasone
CYP2B6	PXR, CAR	
MDR1	PXR, CAR	
OATP8	FXR	FXR: chenodeoxycholic acid

Adapted from Urquhart et al J Clin Pharm 2007;47:566-78

Enzyme Induction

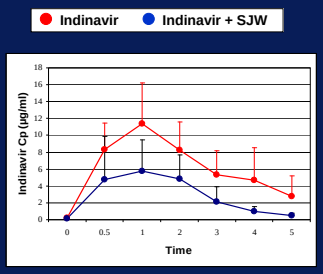


Induction: Influence of Ritonavir on Olanzapine Disposition in Healthy Volunteers



Penzak SR et al. J Clin Psychopharm 2002;22:366-70

St. John's wort: CYP3A4 Induction Effects



- 8 normal volunteers
- Indinavir AUC determined before and after 14 days SJW 300 mg TID
- Indinavir AUC decreased by 57 ± 19% in presence of SJW

Piscitelli SC et al. Lancet 2000;355:547-8

Predicting Drug Interactions: in vitro *Screening*

- Drug development: predicting *in vivo* drug interactions from *in vitro* data Microsomes, hepatocytes, liver slices, purified CYP enzymes etc.
  - Limitations and caveats
    - √ Most systems can only assess inhibition (not induction)
      - – Methadone + ritonavir: discordant *in vivo / in vitro* results
    - √ Hard to extrapolate data when drugs have multiple CYP pathways
    - √ *In vitro* concentrations used may be excessively high
      - – Ritonavir inhibition of MRP2

Predicting Drug Interactions: using CYP phenotypes

- Probe + putative inhibitor or inducer
  - Measure probe (+/- metabolite(s) concentration(s)
  - Ratios of metabolite:parent compound
  - Examples of CYP probes
    - √ CYP1A2: caffeine
    - √ CYP2C9: tolbutamide; warfarin (+ vitamin K!)
    - √ CYP2C19: S-mephenytoin; omeprazole
    - √ CYP2E1: chlorzoxazone
    - √ CYP2D6: dextromethorphan; debrisoquine; sparteine
    - √ CYP3A4/5: midazolam
    - √ CYP3A4: erythromycin

Herb-Drug Interactions Limitations

- **Since not regulated by FDA, safety & efficacy not required**
  - Little information available regarding drug interactions
- **Extrapolation of data to available products difficult**
  - Independent lab tests many products (http://www.consumerlabs.com/)
  - 6/13 SAMe preparations did not pass testing
    - √ no detectable SAMe noted in one product
  - 8/17 valerian preparations did not pass testing
    - √ 4 - no detectable levels of valerenic acid
    - √ 4 - 1/2 the amount claimed on the label

Evaluation of Specific Drug Interactions

- **What is the time-course of the interaction**
  - Immediately or over a period of time
- **Is it a drug class effect**
  - omeprazole vs. lansoprazole
- **Is the interaction clinically significant**
  - Therapeutic index of drugs
    - √ Narrow or wide?
- **How should the interaction be managed?**
  - DC drug? Switch to another drug? Change dose?

Drug Interactions: General Tools for Evaluation and Management

- **Familiarity with metabolic pathways**
- **Know where to locate information on interactions**
- **Obtain thorough medication HX at each visit**
- **Maintain high index of suspicion when:**
  - Therapeutic response is less than expected
  - Toxic effects are present
- **Choose drugs that are less likely to interact**
- **Consider TDM in certain situations (anti-TB TX)**
  - Anti-TB and anti-HIV therapy

Drug Interactions: Resources

THE END

TABLE 5. WEB SITES WITH INFORMATION ABOUT DRUG INTERACTIONS.

www.dml.georgetown.edu/depts/pharmacology (Department of Pharmacology, Georgetown University Medical Center)
www.foodmedinteractions.com (food and drug interactions)
www.hivatis.org (HIV/AIDS Treatment Information Service)
www.hivdent.org (dental information)
hivinsite.ucsf.edu
www.hiv.net (in German)
www.hopkins-aids.edu (Johns Hopkins AIDS Service)
www.iapac.org (International Association of Physicians in AIDS Care)
www.hiv-druginteractions.org (Liverpool HIV Pharmacology Group)

http://hivinsite.ucsf.edu/arvdb?page=ar-00-02&post=7
http://www.naturaldatabase.com

Piscitelli SC, Gallicano KD. Interactions Among Drugs for HIV and Opportunistic Infections. N Engl J Med 2001;344:984-96.

THE END