NNFA Las Vegas 2005
Herb-Drug Interactions

Dr. Arthur M. Presser

President: Huntington College of Heath Sciences

apresser@hchs.edu

Adjunct Assistant Professor of Pharmacy Practice
Curriculum Coordinator Complementary & Alternative Medicine
University of Southern California School of Pharmacy

apresser@usc.edu

Safety

- Perspective
  - 1:20 Bypass
  - 1:250 Medical mishap
  - 1:333 Proper Rx use
  - 1:5000 Auto accident
  - 1:10,000 Murder
  - 1:1,000,000 Herb use

Safety

- "*Not everything that can be counted counts, and not everything that counts can be counted*"— *Albert Einstein*
- An herb is the sum of its parts, not its individual parts
- Almost all warnings are based on "theoreticals" not actual experience.
  - Most often based on a single constituent

***Journal of Pharmacy and Pharmacology*, 2004; 56(8):1039-1044.**

- Components of Ginkgo
  - Terpene lactones (ginkolides) no effect on P450
  - Flavonol aglycones (kaempferol, quercetin, apigenin, myricetin, tamarixetin) ↓ 1A2 and 3A.
  - Quercetin ↓ 2C9

Safety

- With the exception of a few herbal products, most documentation regarding potential drug interactions is based on case reports and often lacks relevant information
- Must differentiate
  - Potential interaction vs. evidence based interaction

Case Report Standards

1. Adequate patient history
2. Concurrent diseases, conditions, or meds presumably are not associated with adverse event
3. Documentation of concomitant meds
4. Adequate descriptions of interactors
5. Exclusion of obvious alternative explanations
6. Complete chronology
7. Reasonable time sequence of drug administration to adverse event
8. Adequate description of adverse event
9. Cessation of event on stopping the drug
10. Recurrence of event with rechallenge

Safety

- What is the level of evidence
  - Animal study
  - Controlled trial
  - Multiple case reports
  - Single case report
  - Pharmacological evidence

Fugh-Berman, A. Ernest E. Herb-drug interactions: Review and assessment of report reliability. *British Journal of Clinical Pharmacology* 2001;52:587-595.

- Medline, Embase, Cochrane Library, CISCOM
- 10 major herbal manufactures
- 8 experts
- 24 organizations
- 4 major reference texts
- 6 recent review articles
- Author's files
- Bibliographies of all articles

Are there herb-drug interactions?

Absolutely!

Who is at risk?

- Populations most susceptible to interactions
  - Cardiac or CVD disease
    - Take drugs with narrow therapeutics windows
    - Anticoagulants, cardiac glycocides
  - Elderly
    - Chronic drugs
  - Diabetics
    - Effects on glucose control
    - Secondary problems warranting drug therapy
  - Depression
    - May be using St. John’s Wort
  - HIV
    - Meds susceptible to interactions
    - Depression

Drug interactions?

- If so what?

- Interactions can be pharmacokinetic
  - Metabolism
- Interactions can be pharmacodynamic
  - Additive effects of similar effects

Are herbs evil?

- Absolutely not!
- Significant risk for patients exists primarily in 3 groups of drugs:
  - Immunosuppressives (cyclosporine)
  - Anticoagulants (warfarin)
  - Protease inhibitors (AIDS)

Drug-Herb Interactions

- Types of Drug Interactions
  - Decreased bioavailability of drug
    - ↓ Absorption (fibers, mucilage herbs, ↑ p-glycoprotein)
    - ↑ Metabolism (↑ CYP 450)
    - ↑ Elimination (laxative or diuretic herbs)
  - Increased bioavailability of drug
    - ↑ Absorption (Ginger, Cayenne, Black Pepper)
    - ↓ Metabolsim (↓ CYP 450, eg. Grapefruit Juice)
    - ↓ Elimination (Licorice- anti-diuretic)

Drug-Herb Interactions

- Types of Drug Interactions Cont.
  - Potentiation of drug via similar activity
    - Eg. Drug diuretic and herb diuretic
  - Potentiation of drug via complementary activity
    - ↓ P-glycoprotein system (eg. Eluthero and antibiotics)
    - Eg. Bitter melon, gymnema, fenugreek,etc. and insulin or oral hyoglycemics

Drug-Herb Interactions

- Types of Drug Interactions Cont.
  - Decreased effectiveness of drug via antagonistic activity
    - Eg. CNS stimulant with CNS depressant
  - Reduced side effects of drug
    - Eg. Milk Thistle and hepatotoxic drugs, Licorice and corticosteroids, Astragalus and chemotherapeutics

Drug-Herb Interactions

- Proactive interaction management
  - Avoid red flags
    - Warfarin
      - Interacts with just about everything
      - 99% protein bound, slightest change can cause problems
    - Digoxin
    - Cyclosporin
    - Protease inhibitors

Drug-Herb Interactions

- Proactive management cont.
  - Use basic knowledge of herb activity to predict potential problems
  - Separate drugs and herbs by 2-3 hours
  - If patient is on a drug regimen and wants to add herb, start with low herb doses and work up
    - Low and Slow

Drug-Herb Interactions

- Understand Phase I liver detoxification
- Function to ↓ harmful compounds
  - Xenobiotics (drugs, pesticides, hormones, bacterial toxins)
- Phase I
  - Directly neutralizes or coverts to intermediates more accessible to Phase II
  - P-450 enzymes (pro-oxidants)
- Phase II
  - Conjugation
    - Binds something to toxin to make it excretable in urine or bile
  - Uses glutathione, sulfates, acetates, cysteine, glucuronic acid

P-450 Enzymes

- Major catalyst of phase I drug biotransformation
- Monooxygenases
- Cyto= cell, chrome= color
- Absorb light at particular frequencies (450nm)
- Various isoforms (isozymes)
  - 16 families and 29 subfamilies
  - Found in smooth endoplasmic reticulum (SER)
    - Liver cells have highly developed SER therefore large proportion of P-450 enzymes
  - 90% of pharmaceuticals metabolized by P-450
    - Isoenzymes most commonly involved in drug metabolism: 3A4, 2D6, 1A2

P450 continued

- Act primarily in liver, but also intestine and other cells.
- Primary role in 1st Pass Metabolism
  - Process of intestinal and hepatic degradation or alteration of a drug taken by mouth, after absorption, removing some of the active substance from the blood before it enters the general circulation.

Drug-Herb Interactions

- CYP families
  - CYP1
    - Drug metabolism
    - Combustion – aromatic hydrocarbons
      - ↑ by cigarette smoke, charred food
    - Converts actives compounds to carcinogens
    - CYP1A2
      - ↓ by Kava (maybe ginkgo)

Drug-Herb Interactions

- CYP2
  - Drug and steroid metabolism
  - CYP2E1
    - Ethyl alcohol to acetaldehydes
    - ↑ by starvation

Drug-Herb Interactions

- CYP3
  - CYP3A4
    - Drug metab (50%)
    - Most abundant in liver
    - ↓ by ketoconazole, progesterone
    - ↑ by acetomenaphen, DM
    - ↑ by St. John's Wort (most work invitro), Guggul, Garlic
    - ↓ by goldenseal
    - ↓ by grapefruit
      - Narginenin, bergamottin - bioflavonoids in juice
      - Decr frist pass metab via CYP3A4, 1A1, 1A2 in intestine
    - ↓ maybe by ginger, kava,, oregano, sage, turmeric (1A1), chamomile, feverfew, eluthero (invitro screening)

Drug-Herb Interactions

- P450 enzymes
  - CPY3A4, CPY3A5, CPY3A7, CPY3A3 most important isoforms for metabolizing drugs
  - Drugs metabolized by CPY3A4 or CPY3A3
    - Amlodipine, astemizole, carbamazepine, clozapine, cyclosporine, diltiazem, 17β-estradiol, ethinyl estradiol, felodipine, imipramine, midazolam, nifedipine, nisoldipine, nitrendipine, saquinavir, quinidine, triazolam, verapamil
  - Note: erythromycin and ketoconazole inhibit CPY3A4

Drug-Herb Interactions

- P-glycoprotein
  - **Located in apical surface of epithelial cells**
  - Found in gut, kidney, brain, liver
  - ATP dependant pump that effluxes poisons out of cells
  - **Interferes with xenobiotic absorption by pumping back into intestine lumen**
  - Cancer cells use to reject chemotherapeutics
  - Bacteria use to become resistant to antibiotics

Drug-Herb Interactions

- St. John's Wort - Just Say No To
  - Cyclosporine
  - Digoxin
  - Protease inhibitors
  - Warfarin
  - Oral contraceptives
    - No reports of unwanted pregnancies
    - Possible breakthrough bleeding
  - Theophylline – not valid
  - SSRIs
  - Irinotecan
  - Imarinib (Gleevec) - ↓ AUC 30%

Drug-Herb Interactions

- Astragalus
  - ↑ immune effects of interleukin-2 and acyclovir
  - May be incompatible with immunosuppressive drugs
    - Cyclosporine
    - Azathioprine
    - Methotrexate

Drug-Herb Interactions

- Bitter Melon
  - ↓ blood sugar
  - Pharmacodynamic
  - Monitor

Drug-Herb Interactions

- Bromelain
  - May ↑ bleeding with anticoagulants
    - Monitor
  - May ↑ effects of antibiotics
  - ↑ efficacy of 5-fluoroiuracil and vincristine

Drug-Herb Interactions

- Cayenne
  - May ↑ metabolism of drugs by enhancing absorption
  - ↓ gastric mucosal damage when taken 30 min before ASA
  - Topical use ↑ ACE inhibitor cough

Drug-Herb Interactions

- Eleuthero
  - ↑ dig levels (interferes with test only)
  - ↑ tolerance to chemo (Russian studies)
  - ↑ effects antibiotics (monomycin, kanamycin)
  - ↑ effects adeturone (radioprotective drug)
  - Possible inhibition of 2C19
  - Possible P-glycoprotein

Drug-Herb Interactions

- Garlic
  - May ↑ bleeding times with anticoagulants
    - 5-20 cloves = 1 ASA
  - ↓ blood levels of protease inhibitor (Saquinavir®)
  - ↑ Indomethacin, insulin, statins
    - Monitor
  - Some garlic preparations containing allicin may increase the activity of 3A4

Drug-Herb Interactions

- Ginger
  - May ↑ absorption of drugs
  - May ↑ bleeding with anticoagulants (?)
  - May ↑ cholesterol lowering effects of statin drugs
  - Case reports of ↓ effect of antacids (heartburn)

Drug-Herb Interactions

- Ginkgo
  - May ↑ bleeding with anticoagulants
  - May ↑ activity and side effects of MAO inhibitors
  - Use with caution with controlled seizure disorders (case report)
  - May ↑ efficacy (potency) of haloperidol in schizophrenia (study)
  - ↑ nifedipine plasma levels (study)

Drug-Herb Interactions

- American Ginseng
  - Hypoglycemic
    - Journal of the American College of Nutrition, Vol.23, No. 3,248-258 (2004)
    - American and Vietnamese lowered 90 min. plasma glucose
    - Panax, Wild American, raised peaks
    - Sugar effect depends on Rb to Rg ratio
      - American his higher in Rb

Drug-Herb Interactions

- Green Tea
  - High in tannin, do not take with codeine or theophylline (inhib absorption)
    - Large amounts may ↑ effects and side effects of theophylline??????????
  - May ↓ effect of coronary vasodilator drugs such as dipyridamle if taken simultaneously
  - Synergistic with sulindac and/or tomaxifen and may ↓ adverse effects
  - Little or no effect on 3A4 or 2D6 *Drub Metab Disposition*. 2004

Drug-Herb Interactions

- Green Tea cont.
  - May ↓ effects of warfarin (Case report)
- **Blood Thinning Medications**
  http://www.daytondailynews.com/health/altmed/shared/health/alt_medicine/ConsHerbs/Interactions/GreenTeach.html
  - Green tea should not be taken with warfarin, a blood-thinning medication, because the herb contains vitamin K and, thus, can render warfarin ineffective.
  - Similarly, green tea and aspirin should not be mixed because they both prevent platelets from clotting. Using the two together, therefore, may increase your risk of bleeding.

Drug-Herb Interactions

- Guggul
  - ↓ efficacy of beta blockers and calcium channel blockers
    - Study
  - In Vitro ↑ 3A4

Drug-Herb Interactions

- Kava
  - ↑ actions of depressant drugs, alcohol
  - Contraindicated with hepatotoxic drugs and alcohol
  - ↓ efficacy of Parkinson drugs (L-Dopa)
  - ↓ 3A4, isolated kavalactones
    - No systematic studies on pharmacokinetic interactions
    - No unequivocal clinical evidence; In vitro studies based on theoretical considerations

Drug-Herb Interactions

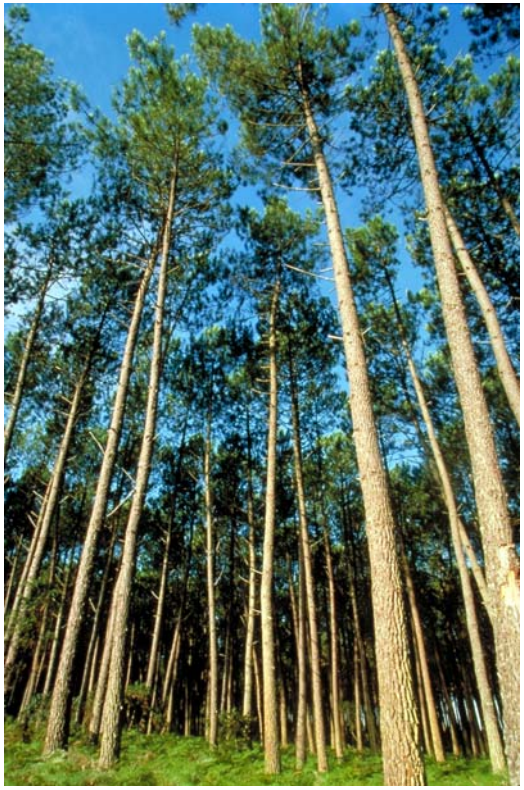
- Licorice
  - ↓ efficacy ↑ toxicity of diuretics
    - Large doses ↓ K
  - ↓ efficacy and ↑ side effects of digoxin
    - Large doses ↓ K, Low K ↑ risk or dig toxicity
  - Potentiates corticosteroids
  - ↑ blood pressure (pseudoaldosteronism)

Drug-Herb Interactions

- Milk Thistle
  - ↓ hepatotoxicity of drugs
    - APAP, haloperidol, halothane, dilantin, butyrophenones, and phenothiazines, phenytoin
  - ↓ kidney toxicity (without reducing actions) cisplatin and doxorubicin
  - ↓ kidney toxicity of anesthetics
  - Contrary to previous reports- little or no effect on 3A4 or 2D6 [*Clin Pharmacol Ther*, 2004;75(2):35]

Drug-Herb Interactions

- Pycnogenol and nifedipine (Procardia, Adalar) calcium channel blocker
  - Life Sciences. 2004;74:855-862
  - 100mg per day, 12 week trial
  - Pycnogenol group needed aprox 40% less drug (P<0.001)
  - Researchers believe that Pycnogenol shifts balance of vasodilatation and vasoconstriction in the direction of vasodilatation
    - Lowers endothelin-1 (compound that triggers vasoconstriction)
    - Raises 6-ketoprostiglandin F1 (compound relaxes blood vessels)
  - Pycnogenol improves function of the endothelium (lining of blood vessels)



Drug-Herb Interactions

- Schizandra
  - ↓ cardiotoxicity of adriamycin
  - ↓ CNS stimulation of caffeine and amphetamines
  - ↓ hepatotoxicity of drugs (including APAP)
  - May ↑ action of pentobarbital

Drug-Herb Interactions

- Valerian
  - ↑ effects of CNS depressants
    - Phamracodynamic
  - *Drug Metab Dispos*. 2004;32::1333-1336
    - Minimal effect of 3A4 and no effect on 2D6
      - DM (2D6) metabolized extensively to its metabolite before and after Valerian dosing.
      - Alprazolam (3A4) not significantly altered after Valerian dosing.

Thank You – Questions?

huntington college of HEALTH SCIENCES

Accredited distance learning institution

www.hchs.edu • 800-290-4226

1204-D Kenesaw • Knoxville, TN 37919

E-mail: studentservices@hchs.edu