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Risk of Drug Interactions Involving Herbal and Citrus Products

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Adverse Drug Reactions—Marketed Drugs

- 2,000,000
  number of serious ADRs yearly

- 100,000
  annual number of ADR-related deaths

- 4-6
  ranking of serious ADRs as causes of death

- 136,000,000,000
  annual cost in dollars associated with ADRs

Why are there so many ADRs?

Use of Medications by Sex and Age
• Use of botanicals has increased
• One in five Americans (18.4%) take prescription medications concurrent with at least 1 herbal product, a high-dose vitamin, or both
• 15 millions are at risk for potential adverse interactions (including 3 millions 65 years or older)

< Eisenberg DM et al., JAMA 280 (18): 1569, 1998>
Evaluation of Drug-Drug Interactions?

-When are they significant-
Tools available


- “Drug Interactions in Drug Development” website (expected one-line 1Q 2006)
  <http://www.fda.gov/cder/drug/drugInteractions/default.htm>

Key messages:
1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish “Therapeutic equivalence boundaries” (no effect boundaries)
5. Labeling language needs to be useful and consistent
Key Questions To Ask On Drug-Drug Interactions:

1. Will an NME alter exposure to other drugs

2. Will other drugs alter exposure to the NME?

3. Are these alterations in exposure significant enough to warrant dose adjustment?
Labeled dose, AUC, or effective concentration (100%)

80% 170%

Efficacy Curve

Therapeutic Range

Safety (Adverse Effect) Curve

Labeling Impact
- Drug-Drug Interactions -

- Concomitant Medications: The dosage of LEVITRA may require adjustment in patients receiving certain CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, indinavir, and erythromycin) (see WARNINGS, PRECAUTIONS, Drug Interactions).
Labeling Impact
- Drug-Drug Interactions (2) -

- For ritonavir, a single dose of **2.5 mg LEVITRA** should not be exceeded in a **72-hour** period.
- For indinavir, ketoconazole 400 mg daily, and itraconazole 400 mg daily, a single dose of **2.5 mg LEVITRA** should not be exceeded in a **24-hour** period.
- For ketoconazole 200 mg daily, itraconazole 200 mg daily, and erythromycin, a single dose of **5 mg LEVITRA** should not be exceeded in a **24-hour** period.
Evaluation of Drug-Herb Interactions?
-When are they significant-
Key Questions To Ask On Drug-Drug Interactions:

1. Will an NME alter exposure to other drugs?

2. Will other drugs alter exposure to the NME?

3. Are these alterations in exposure significant enough to warrant dose adjustment?

Questions on Drug-Botanical Interactions
Evaluation of Drug-Herb Interactions?
-Which herbs-

- Case reports
  - systematic evaluation of reports

- Specific studies to understand mechanisms of interactions
  - herb’s effects on specific drugs
  - herb’s effects on specific probes for enzymes and transporters
  <in vitro and in vivo studies>
St John’s Wort
St John’s wort (2)

- Cases of rejection of heart transplant patients on St John’s wort

- Up to 2001, FDA’s Adverse Event Reporting System (AERS) in CDER indicated up to 39 case reports


<Chen M, Drug-Herb Interactions, Eds. Lam, Huang, Hall, Taylor & Francis, in press>
St John’s wort (3)
-effect on CYPs-

• St John’s wort decreased indinavir plasma levels

• **Acute** St John’s wort had little effects on major CYPs (CYP1A2, 2D6, 2C9, 3A)
• **Chronic** St John’s Wort induced CYP3A

St John’s wort (4)
- Effect on P-gp -

- Fexofenadine levels were *slightly increased* by acute St John wort dosing and *reduced* during chronic dosing

- Consistent with an increase in immunodetectable CYP3A4 and P-gp in intestinal biopsies following 14 days treatment with St John’s wort (Dürr et al., CPT 68, 598, 2000).

St John’s wort (5)
- Effect on OC -

• 8 weeks of St John’s Wort decreased norethindrone levels and ethinyl estradiol t1/2

• More breakthrough bleeding occurred in St John’s Wort phase

• Higher midazolam clearance for those with breakthrough bleeding (216+ 67 vs. 98 +37)

St John’s wort (6)

• Case reports
  - systematic evaluation of reports

• Specific studies to understand mechanisms of interactions
  - herb’s effects on specific drugs
  - herb’s effects on specific probes for enzymes and transporters
  <in vitro and in vivo studies>
St John’s wort (7) - Regulatory Impact -

- FDA Health Advisory on “concomitant use with protease inhibitors or NNRTI is not recommended”
  <http://www.fda.gov/cder/drug/advisory/stjwort.htm>

- Labeling revision of marketed drug products

- Labeling of newly approved drugs
When do we include St. John’s Wort in the drug labeling?

Cytochrome P450 3A and/or P-gp substrates and where the products' effectiveness may be reduced upon co-administration of St. John's Wort
Current Labeling
- St John’s wort -

- 55 drug products with St John’s wort in the labeling
  - 2 based on actual clinical studies
  - others based on reports and/or mechanistic reasons
  - 2 not related to the products (concurrent OC use)

< As summarized in Huang S-M, Lesko, LJ, Temple R, in “Herb-drug interactions”, eds, Lam, Huang, Hall, Taylor & Francis, in press>
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
PRECAUTIONS: Herbal products containing St. John’s Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Other botanical products?

- Echinacea selectively modulates the catalytic activity of CYP3A at hepatic and intestinal sites.

- The type of drug interaction observed between echinacea and other CYP3A substrates will be dependent on the relative extraction of drugs at hepatic and intestinal sites.

- Study to evaluate the effects on OC ongoing

Other botanical products?

• Ginkgo Biloba extract induced CYP2C19

• AUC ratio (omeprazole/5-OH omeprazole) decreased by 68%; the extent of interactions appear to be CYP2C19 genotype-dependent

<Yin OQ et al, Pharmacogenetics, 2004 Dec;14(12):841-50>
Protocol Design

How do we address possible drug dietary supplement interactions?

Clinical protocol- Participants will be excluded for the following reasons:
..... use of prescription or over-the-counter medications, *including herbal products*, or alcohol within two weeks prior to enrollment;

<Protocol for FDA/Indiana echinacea- cytochrome P450 interaction study; results in Clin Pharmacol 2004 Jan;75(1):89-100 >
Interactions with Citrus Fruit/Juices

Grape fruit juice
Grapefruit Juice - Drug Interactions

% AUC increase over baseline

-100 -500 0 500 1000 1500 2000 2500 3000 3500 4000 4500 5000

Fexofenadine, itraconazole, pravastatin, cyclosporine, nimodipine, midazolam, triazolam, saquinavir, atorvastatin, felodipine, terfenadine, misoprostol, bupirone, lovastatin, simvastatin

900, 1500, 1600%
Grapefruit Juice
Post-marketing reports (FDA)

- Up to 2004, FDA’s Adverse Event Reporting System (AERS) in CDER indicated up to 40 case reports
Case Report

Lovastatin and Grapefruit Juice (1)

• 60 yo male with hypertension, chronic lower extremity venous stasis/edema, renal insufficiency, non-insulin dependent diabetes mellitus and familial history of hyperlipidemia

• taking lovastatin concurrent with gemfibrozil, amlodipine, metoprolol, glyburide, trovafloxacin, vitamine E, metformin, aspirin, ciprofloxacin

• changed his usual orange juice to grapefruit juice

• muscle pain and high CPK (>40, 000 U/L)

<Piazza-Hepp, T, in “Herb-drug interactions”, eds, Lam, Huang, Hall, Taylor & Francis, in press>
Case Report
Lovastatin and Grapefruit Juice (2)

- ICU for rhabdomyolysis with acute renal failure, overlapping with chronic renal failure
- started IV fluid; d/c lovastatin and gemfibrozil; creatinine (5 mg/dL); gradually back on other meds
- CPK to 1,017; improved on muscle weakness
- Physician concluded drug interactions between grapefruit and lovastatin and gemfibrozil
=> told the patient to avoid grapefruit juice
Case Report

Nifedipine and Grapefruit Juice

• 92 yo female with hypertension took nifedipine 30 mg daily for 4 years

• while traveling in Florida, took nifedipine with grapefruit juice: experiences extreme fatigue, dizziness, vertigo, decreased appetite, disorientation

• hospitalized, juice stopped, recovered

• Back home, took nifedipine with grapefruit juice again, experiences a similar but milder grapefruit and lovastatin and gemfibrozil

  => pharmacist suspected an interaction between nifedipine and grapefruit juice
Current Labeling
- Grapefruit juice -

- 35 drug products with grapefruit juice in the labeling
- 50% reported clinical data
- others based on reports and/or mechanistic reasons
- grapefruit juice considered “moderate CYP3A inhibitor”- CYP class labeling

< As summarized in Huang S-M, Lesko, LJ, Temple R, in “herbal-drug interactions”, eds, Lam, Huang, Hall, Taylor & Francis, in press>
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Regulatory Impact

When do we include grapefruit juice in the drug labeling?

Cytochrome P450 3A substrates with low oral bioavailability (due to enteric first pass)

Dosage and Administration:
Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine (Neoral), thus should be avoided.

Warnings/Precautions:
To avoid possible serious side effects, avoid drinking large quantities of grapefruit juice (more than one quart daily) while on simvastatin (ZOCOR) (see ....Muscle)

<http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57301293.htm#PDRCON01, 11/99 update>
Health Canada on GFJ

• Certain drugs and health products used in the treatment of the following medical conditions are known to cause this effect: Angina; Anxiety; Cancer; Convulsions; Depression; Erectile dysfunction; Gastrointestinal reflux; High blood pressure; High lipid (cholesterol) levels; HIV/AIDS; Infections; Irregular heart rhythms; Organ graft rejections; Psychotic problems

• if you are taking medication for any of the conditions listed above, DO NOT drink grapefruit juice or eat grapefruit in any form, until you have talked to your doctor and your pharmacist about the potential for an adverse reaction.

• Avoid taking any drug with grapefruit juice until you have asked your doctor or pharmacist if it is safe to do so.

Interactions with Citrus Fruit/Juices
- Effects on *transporters*

Grapefruit juice/
Apple juice/
Orange juice
Effect of various juices on fexofenadine (n=10) in a randomized 5-way crossover

Effect on OATP > P-gp?

(1.2 L over 3 hours) in a randomized 5-way crossover

Other interactions with citrus fruit
Calcium-fortified Orange juice

Evaluation of -floxacins from various studies (n=15-16)

Other interactions with Cranberry Juice

September 2003, "Current Problems in Pharmacovigilance“ by British Committee on Safety of Medicines

- patients taking warfarin *should limit or avoid* drinking cranberry juice

- five reports; one fatal-- involved a man whose INR >50 six weeks after starting cranberry juice

*Effect on CYP2C9?*

Protocol Design

How do we address possible drug-juice interactions?

“For at least two weeks prior to the start of the study until its conclusion, volunteers will not be allowed to eat any food or drink any beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard) and charbroiled meats.”
Related to Drug-Natural Product Interactions:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish “Therapeutic equivalence boundaries” (no effect boundaries)
5. Labeling language needs to be useful and consistent

NME’s clearance pathway needs to be well-defined
Studies may not be needed - from known info
NME’s exposure-response needs to be well-defined
## Drug Interactions working group

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Questions?
Update on Botanical IND’s
Botanical Applications in FDA
(as of June 1, 2005)

- Total of 242 Applications
- 192 INDs (2/3 active); 50 pre-INDs
- 50 in ‘90-’98, 192 in ‘99-’05
- 2~3 new subm/month in recent yrs
- 40% commercial, 60% research
- 2/3 single herb, 1/3 multiple herbs
Botanical Applications at FDA Growing over the Years

Botanical Applications 1982-2005

- Annual Ave
- Period Total

1982-89  1990-94  Jan '95 - July '00  Aug '00 - May '04  Jun '04 - May '05

<Shaw Chen, CDER, FDA, November 2005>
Botanical Applications in FDA

Botanical Applications by Therapeutic Classes

<Shaw Chen, CDER, FDA, November 2005>
Drug-Drug Interactions
- Labeling Implications -
• All relevant information…. should be included in the PHARMACOKINETICS subsection of the CLINICAL PHARMACOLOGY section of the labeling.

• The clinical consequences …. should be placed in DRUG INTERACTIONS, WARNINGS AND PRECAUTIONS, BOXED WARNINGS, CONTRAINDICATIONS, or DOSAGE AND ADMINISTRATION sections, as appropriate.

• When the data resulted in recommendations for dosage adjustments, contraindications, warnings, these recommendations should also be included in “HIGHLIGHTS.”
Drug- Natural Product Interactions
- Current Labeling examples -

Physicians’ Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian
Cyclosporine

DOSAGE & ADMINISTRATION

*Grapefruit and grapefruit juice* affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.
Fexofenadine

Interactions with Fruit Juices

*Fruit juices such as grapefruit, orange and apple* may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. ........ Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR *should be taken with water*

Levonorgestrel and Ethinyl Estradiol

Herbal products containing St. John's wort (Hypericum perforatum) may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Isotretinoin

CONTRAINDICATIONS and WARNING

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort (see PRECAUTIONS).*1
Warfarin

PRECAUTIONS

Caution should be exercised when *botanical medicines (botanicals)* are taken concomitantly with COUMADIN. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to *monitor the patient’s response with additional PT/INR determinations when initiating or discontinuing botanicals.*

Warfarin (2)

Information for Patients

Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics), other over-the-counter medications, and **botanical (herbal) products** (e.g., bromelains, coenzyme Q10, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John’s wort) except on advice of the physician.

St John’s wort Products

WARNING: St. John's Wort can have potentially dangerous interactions with some prescription drugs. Consult your physician before taking St. John's Wort if you are currently taking anticoagulants, oral contraceptives, antidepressants, anti-seizure medications, drugs to treat HIV or prevent transplant rejection, or any other prescription drug.

FTC Warning ON Herbal Outlook or similar product (Panda), St. John's Kava Kava (ForMor), http://www.ftc.gov/opa/2001/06/cureall.htm
References for Draft Guidance on Drug Interactions


• Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103


• Yuan, Madani, Wei, Reynolds, Huang, Drug Metab Disp, December 2002; 30(12) 1311


• FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues and challenges in the evaluation and labeling of drug interaction potentials of NME. Rockville, MD. April 23, 2003; http://www.fda.gov/ohrms/dockets/ac/03/slides/3947s2.htm; http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3947T2.htm


• Huang S-M, Lesko LJ, J Clin Pharmacology, June 2004


• CDER Drug Interactions Website (available 1Q; http://www.fda.gov/cder/drug/drugInteractions/default.htm )