

Herb-drug interactions



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Outline

- ▶ Evidence for herb-drug interactions
- ▶ Pharmacokinetic (PK) versus pharmacodynamic (PD) interactions
- ▶ St. John's wort
- ▶ Warfarin
- ▶ Miscellaneous
- ▶ Herb-drug interactions and surgical/dental procedures
- ▶ Use of computer databases for clinical questions

Learning objectives

- ▶ Distinguish between pharmacokinetic and pharmacodynamic interactions.
- ▶ Know the principal pharmacokinetic and pharmacodynamic interactions of St John's Wort, i.e. induction of CYP450 3A4, and serotonin syndrome/photosensitivity
- ▶ Know the main reasons for herb-drug interactions with warfarin, i.e. vitamin K activity; decreased GI absorption or CYP450 2C9 metabolism and herbs that decrease platelet aggregation or thromboxane synthesis or have coumadin content.
- ▶ Know the main reasons for caution with herbs and surgery or dental procedures, i.e., herbal anticoagulants (cause bleeding), sedative or stimulant herbs (modify anesthesia).

Evidence for herb-drug interactions

- ▶ Case reports
 - Underreported? 70% "don't ask-don't tell"
- ▶ Lab studies
 - Define mechanisms
 - ▶ Recent interest in CYP450 induction
 - ▶ Not necessarily borne out in trials
- ▶ Human studies
 - Trials using probe drugs
 - May be too short or expensive
 - May be done on healthy population (not always)
 - Genetic polymorphisms
 - Multiple drug/herb users, elderly patients

De Smet, Br J Clin Pharm 2006; 63:258-67

Drug Interaction Resolution

- ▶ Require dosage adjustments
- ▶ Temporary or complete elimination of one or the other agent to avoid serious consequences
- ▶ Close monitoring of the subject
- ▶ Total change of drug therapy

PK vs PD

- ▶ PK: absorption, distribution, metabolism, elimination
 - CYP450, Pgp
 - Absorption from GI tract (laxatives)
- ▶ PD: pharmacological function
 - Anticoagulant drugs plus anticoagulant herbs
 - Sedative herbs plus anesthesia
- ▶ Negative
 - Most
- ▶ Positive or synergistic
 - Possible PD or PK
 - Decrease side effects

Prevalence: unknown but under investigation

- ▶ Canadian seniors with osteoarthritis
 - Survey, n = 191. Average 2.8 prescriptions, 1.9 self-care products
- ▶ Potential interactions detected using standard databases
 - 214 instances, 14% possible clinical significance
 - 7 herbs/supplements, associated with 5 clinically insignificant interactions
 - 1 recommendation to stop medications (diltiazem + atorvastatin -> statin side effects intensified)
 - Clinically significant interactions may be rare – but thus easier to forget about and harder to monitor!

Putnam, Can Fam Physician 2006; 52:340-45

St. John's wort (*Hypericum perforatum*)

- ▶ Mild-moderate depression -> long-term treatment; multiple clinical trials, fewer AEs than conventional drugs
- ▶ Case reports suggesting PK interactions (most important of SWJ interactions)
- ▶ Lab studies indicate PK interactions:
 - ▶ CYP450 3A4 mechanism
 - ▶ short-term inhibition
 - ▶ Long-term induction; of most importance clinically
 - ▶ Reduces various drugs to subtherapeutic levels
 - ▶ Hyperforin, an active constituent, is a ligand for the xenobiotic pregnane X receptor -> CYP450 3A4

St John's wort



- ▶ Other PK interactions
- ▶ P-glycoprotein (PgP): involved in multidrug resistance, acts as a pump to remove drugs from cells
 - SJW induces this orphan nuclear receptor
 - Also regulates MDR-1 (multidrug resistance gene) and other drug transporters

Chavez, Life Sci 2006; 78:2146-57

St. John's wort: PK interactions

- ▶ Human trial with irinotecan (cancer)
 - Blood levels of active metabolite were reduced
- ▶ Other drugs affected
 - Cyclosporin, tacrolimus, indinavir, nevirapine, imatinib, alprazolam, midazolam, amitriptyline, digoxin, fexofenadine, methadone, omeprazole, theophylline, verapamil, etoposide.
 - Human study with oral contraceptives indicating reduce OC exposure and breakthrough bleeding.
 - Case of delayed emergence from general anesthesia observed.
 - Multiple potential interactions with oncology drugs (but rare use by oncology patients?).
- ▶ Other CYP450s
 - May inhibit CYP1A2, does not inhibit CYP2D6

Murphy Contraception 2005; 71:402-8

St. John's wort

- ▶ PD interactions
 - With other antidepressants
- ▶ Serotonin syndrome
 - SJW has both SSRI and MAO inhibitor activity
 - Restlessness, nausea, vomiting, tachycardia, hallucinations etc.
 - Case reports with buspirone, loperamil, nefazodone, paroxetine, sertraline, venlafaxine
- ▶ Possible adrenergic crisis
 - MAO inhibitor activity
- ▶ Photosensitivity
 - Active constituent hypericin is photosensitizing but generally not a problem with healthy persons.
 - Potential interaction with other photosensitizing drugs

Clinical strategy

- ▶ Avoid use with other medications unless checked out in an interaction database. Will have similar interaction profile to other CYP450 3A4 inducers.
- ▶ Major drug-drug interaction pathway

Warfarin-herb interactions

- ▶ Numerous drug-drug interactions: macrolides, NSAIDs, COX2s, SSRIs, omeprazole, 5FU etc (variable quality of evidence).
- ▶ Possible pathways: Vitamin K activity lowers INR
 - Foods: leafy greens (healthy diet)
 - "Green drinks" – clinical interactions with oncology patients. Case reports with cranberry juice also.
 - Multivitamins
 - CoQ10: similar structure to vitamin K, but RCT found no effect on INR. Case reports suggest monitoring.

Rhode, Curr Opin Clin Nutr Metab 2007; 10:1-5
Engelsen, Throm Hemost 2002; 87:1075-6

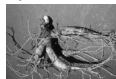
Warfarin-herb interactions

- ▶ PK
 - decreased absorption from GI tract due to mucilage (comfrey, Iceland moss) or laxative herbs (senna, rhubarb etc)
 - CYP450 2C9 inhibition/induction, which metabolizes the active S-enantiomer of warfarin
- ▶ PD
 - herbs that decrease platelet aggregation
 - Decreased thromboxane synthesis
 - Herbs with coumarin content (though this is a relatively weak anticoagulant)

Warfarin and Chinese herbs

- ▶ Dan-shen (*Salvia miltiorrhiza*) – animal studies, case reports
- ▶ Dong quai (*Angelica sinensis*) – animal studies, case reports
- ▶ Asian ginseng (*Panax ginseng*) – ginsenosides may inhibit platelet aggregation (anticoagulant). 2 case reports of lowered or unsteady INR (procoagulant)
 - RCT in healthy volunteers showed no effect of Asian ginseng on INR, platelet aggregation. Vitamin K in extracts? Monitor closely.
- ▶ American ginseng (*Panax quinquefolius*) – RCT in healthy volunteers indicated moderately reduced INR, warfarin levels, AUC. Avoid with warfarin.

Chavez, Life Sci 2006; 78:2146-57
Jiang, Br J Clin Pharm 2004; 57:592-9
Yuan, Ann Intern Med 2004; 141:23-7



Warfarin and "G" herbs



- ▶ Garlic (*Allium sativum*) – 2 case reports. Continuing ingestion of high levels of garlic or garlic oil can decrease platelet aggregation
- ▶ Ginger (*Zingiber officinalis*) – Inconclusive results in studies in healthy volunteers but case reports exist.
- ▶ Ginkgo (*Ginkgo biloba*) – Ginkgolide B decreases PAF, extract inhibits thromboxane and prostacyclin in diabetics. Preliminary human study indicates no effect on INR, but a case report suggests interaction
- ▶ Green tea (*Camellia sinensis*) – Inhibits platelet synthesis of thromboxane. Case report of decreased INR in patient drinking 1 gal/day green tea.

Chavez, Life Sci 2006; 78:2146-57

Warfarin and lipid-based agents

- ▶ Omega-3 fatty acids (fish oil, algal formulas) – case report of increased INR with fish oil in a stabilized warfarin patient, 67-y/o female.
 - Strong antiinflammatory effects, but did not affect INR in an RCT.
- ▶ Saw palmetto – lipid extract. Case report of intraoperative hemorrhage (w/o warfarin) and increased INR in 2 warfarin patients.



Chavez, Life Sci 2006; 78:2146-57

Case Report

Female, age 76, hx of hypertension, osteoarthritis, gastropathy due to NSAIDs, atrial fibrillation, stroke: presents at ER with hematuria and bleeding gums.

Meds: hydrochlorothiazide, warfarin, acetaminophen. No recent illnesses, antibiotics, diet change reported.

CBC normal, previous INR was 2.1 but now 7.0

Case Report

Appropriate INR for stroke patients is 2.0-3.0. Elderly are at risk for bleeding d/t lower body weight, low vitamin K intake, drug interactions.

Drug interactions include acetaminophen (not widely recognized): metabolized by 2C9, as is warfarin.

Patient recently increased acetaminophen intake d/t osteoarthritis flare; cautioned to reduce dose, use daily (not intermittently) and monitor INR more frequently.

Case Report

INR at a therapeutic level for 6 m.

Patient then returned with nosebleed and INR of 10.

Acetaminophen, aspirin, warfarin doses had remained the same, no illnesses.

Closer questioning revealed use of ginger for upset stomach – ginger tea and ginger root.



Case Report

Patient advised to stop ginger consumption & monitor INR more frequently; excessive anticoagulation stopped with iv vitamin K.

Problem: ginger did not cause CYP₄₅₀ interaction in pharmacodynamic/pharmacokinetic study and trials in healthy patients indicated only questionable clinical effect on coagulation

Combined effect of ginger anticoagulant effect and acetaminophen 2C9 effect? Patient age?

Very similar story for chamomile.

Lesho EP et al. Cleve Clinic J Med 2004; 71:651-655
Segal R et al. CMAJ 2006; 174:1281-2

Garlic (*Allium sativum*)

► Drug Interactions:

- Alters pharmacokinetic variables of acetaminophen
- Decreases blood concentrations of warfarin
- Produces hypoglycemia when taken with chlorpropamide (oral antidiabetic)



Izzo AA, Ernst E. Drugs, 2001, 61:2163-2175

Garlic (*Allium sativum*)

► Drug Interactions:

- Saquinavir (Fortovase) study-10 healthy volunteers
- Dose of 1200 mg 3 times daily for 4 days
- AUC during the 8 hour dosing interval decreased by 51%
- 10 day wash out needed before Cmax, AUC levels returned to 60-70% of normal
- Garlic and Protease Inhibitors

Clin Infect Dis, 2002, 34:234-238.

Ginkgo

Case reports of interactions:

- Aspirin – hyphema (blood in eye)
- Acetaminophen - bilateral subdural hematomas
- Warfarin - intracerebral hemorrhage
- Ibuprofen added to ginkgo supplementation was followed by cerebral hemorrhage
- Valproate: 2 cases of seizures
- Possible induction of CYP2C19 and CYP450 3A4, but studies have conflicting results



Kava (*Piper methysticum*)

- ▶ One case report of coma induced by a combination of kava and alprazolam-a benzodiazepine
- ▶ Extrapyramidal side effects-4 cases of dopamine antagonism-oral, lingual and trunk dyskinesia
- ▶ Do not combine with alcohol, sedatives, tranquilizers



Licorice (*Glycyrrhiza glabra*)

- ▶ Sore throat, dyspepsia, peptic ulcer disease
- ▶ Triterpene saponins-glycyrrhizin
- ▶ Prolonged use > 6weeks of >50 g/day-pseudaldosteronism
 - Potassium depletion, sodium retention, edema, hypertension and weight gain
- ▶ Drug Interactions
 - Thiazide and loop diuretics, cardiac glycosides
 - Antihypertensives
 - Spironolactone or amiloride
 - Only clinically significant in cases of excessive use, however... commonly licorice candy
 - Possible with multiple use of herbal formulas containing licorice (ie in Chinese formulas)

Herbal laxatives

- ▶ Decrease blood levels of drugs by shortening gastrointestinal transit time
- ▶ Increase potassium loss
- ▶ Common herbal laxatives: aloe, cascara sagrada, rhubarb, senna

Abebe W, 2003. J Dental Hygiene 77(1):37-46

Oral herb use side effects

- ▶ Feverfew (*Tanacetum parthenium*): mouth sores and irritation if leaves are chewed
- ▶ Feverfew, ginkgo: gingival bleeding due to anticoagulant effect
- ▶ Echinacea (*Echinacea purpurea*) and kava (*Piper methysticum*): tongue numbness
- ▶ St John's wort: xerostomia
- ▶ Yohimbine (*Pausinystalia yohimbe*): salivation

Surgery and Dental Procedures

Drug interactions and physiological reactions:

CNS herbs: potential PD interactions with anesthesia:

Valerian, kava, St. John's wort (PK interaction also), lavender, passionflower, lemon balm, ashwaganda, ginseng, ephedra (now illegal but may be available elsewhere).

Blood sugar – ginseng, bitter melon, chromium, fenugreek, cinnamon

Ang-Lee, JAMA 2001; 286:208-16

Surgery and Dental Procedures

Anticoagulant herbs: post-op bleeding and interaction with aspirin or other NSAIDs that may cause bleeding.

Garlic, ginger, ginkgo, ginseng, feverfew.

Angelica, asafoetida, anise, astragalus, arnica, bogbean, bromelain, borage seed, capsicum, clove, curcumin, dong quai, fenugreek, fish oil, green tea, horsechestnut, juniper, licorice, meadowsweet, onion, pau d'arco, parsley, passionflower, quassia, red clover, reishi, salvia, turmeric, willow.

Surgery and Dental Procedures

Stop herb and supplement use 7-14 days prior to surgery.

All pre-surgical patients should be questioned about herb/supplement use to determine recent consumption of anticoagulant or drug-interacting herbs.

Clinical coping

- ▶ Counteract "don't ask-don't tell"
 - Open and nonjudgmental discussion
 - Follow up herb use found in case histories
 - Explain importance of potential interactions
- ▶ Avoid SJW and warfarin interactions
- ▶ Patients on complicated medical regimens should avoid herbs and supplements unless carefully screened/supervised
- ▶ Package inserts

Checking for herb-drug interactions

- ▶ Natural Standard
(www.naturalstandard.com). Subscriptions for PDA/desktop available.
 - Partial database at MedlinePlus.gov
- ▶ Natural Medicines Comprehensive Database
(www.naturaldatabase.com). Subscription service.

