

Auburn Healthlink

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Medication Safety

MIXING IN HERBALS

It is estimated that 40% -50% of people seeking medical attention are also taking herbal products.¹ Therefore, millions of consumers may be at risk for potential, unintended interactions involving prescription medications and herbs or high dose vitamins. There has been little evaluation of interactions between regulated drugs and herbs, but knowledge of some adverse reactions and therapeutic actions of herbal medicines can help in predicting drug interactions. Concurrent use of herbals and prescription products may result in an amplified, diminished, or antagonistic effect. Table I (see page 2) lists herbs that have been known to interact with commonly prescribed drugs.² Increased awareness of possible interactions can help lessen the risk of serious injury due to herbal product use.

There are certain patient populations in which use of herbals is discouraged. These include pregnant patients or those considering pregnancy, the very young, and the elderly. Patients need to be advised that herbal products should not be used in larger than recommended doses or for long periods of time. Long-term safety data is usually lacking and does not support such use. Continued research is necessary to elucidate the pharmacological activities of the many herbal products on the market today. In response to this need, the National Center for Complementary and Alternative Medicine (NCCAM), a division of the National Institutes of Health (NIH), was mandated by Congress in 1998 to "facilitate the evaluation of alternative medical treatment modalities."³ The NCCAM supports and conducts research on herbal products to determine their safety and efficacy.

Only 30% of patients using herbals disclose their use to physicians and pharma-

cists.⁴ Many patients believe that natural products are harmless and are unaware of the possibility of herbal-drug interactions. A thorough medication history must include patient use of herbal and nutritional supplements in order to ensure safe and efficacious use of prescription agents. Documentation of herbal use and any adverse experiences associated with use may prevent undesirable medication outcomes. It is important to stress to all patients that an accurate diagnosis and discussion of proven treatment options should be explored prior to considering any type of herbal treatment.

References:

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INCREASED PRESCRIBING OF COX-2 INHIBITORS: IS IT JUSTIFIED?

Since the release of the new class of nonsteroidal anti-inflammatory agents, COX-2 selective inhibitors, there has been vast over-utilization of the new class. During 2000, sales of the two COX-2 inhibitors, Celebrex[®] (celecoxib) and Vioxx[®] (rofecoxib), have been staggering. Celecoxib is being prescribed at a rate of 400,000 times per week.¹ Rofecoxib had over two billion dollars in sales during 2000.² Due to the excessive cost of these agents, a more conservative approach to prescribing COX-2 inhibitors is needed. Although they have a few advantages over traditional NSAIDs, these advantages should only increase their utility in certain patient populations.

Over the past two years, there has been an increase in the prescribing of COX-2 selective inhibitors. The total amount of prescriptions written for celecoxib increased by 162% during the past year.¹ The increase in overall drug cost caused by prescribing COX-2 inhibitors, as opposed to traditional NSAID therapy, is almost a factor of ten. The average cost of one month of ibuprofen, 600 mg three times a day, is less than \$10, while the cost of celecoxib 200 mg per day or rofecoxib 25 mg per day is over \$70 per month. Thus, over the course of one year, an average patient, or their health benefit provider, would spend around \$700 more for a regimen that offered a comparable safety profile and similar efficacy.

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Recent trials have demonstrated that COX-2 selective inhibitors demonstrate less pronounced effects on renal function, the GI mucosa, and platelet aggregation. Rossat et al. examined the effects of celebrex and naproxen on renal function in 40 middle aged, salt-depleted patients. The researchers found that selective inhibition of COX-2 has similar effects on water and sodium excretion as naproxen. Thus, during states of salt-depletion, when renal function is more dependent on prostaglandin synthesis, COX-2 selectivity does not appear to spare renal function.³ Swan et al. examined the effects of COX-2 inhibition versus nonselective COX inhibition on the renal function of 71 elderly patients receiving a low-salt diet. The researchers observed that the decrease in glomerular filtration rate (GFR) with selective COX-2 inhibition was similar to that of nonselective inhibition.⁴ Whelton et al. compared the effects of naproxen and celecoxib on renal function in 29 healthy elderly subjects. The researchers found a statistically significant difference in the amount of reduction in GFR between the two study groups. Naproxen decreased GFR by 7.5 ml/min, in contrast to a 1 ml/min reduction by celecoxib. They also found that celecoxib had effects similar to naproxen on renal prostaglandin excretion and sodium retention. The authors concluded that COX-2 selective inhibition spares the renal hemodynamic function of

the kidney.⁵ Although the difference in these effects may be statistically significant in this small trial, the clinical relevance has yet to be proven.

With respect to COX-2 selectivity and gastrointestinal damage, there have also been numerous trials published in the past few years. Watson et al. found that rofecoxib was associated with a lower incidence of treatment discontinuations due to GI adverse events over twelve months and a lower incidence of dyspeptic-type GI adverse events over six months than nonselective COX inhibitors or NSAIDs.⁶

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Silverstein et al. observed that at dosages greater than those indicated clinically, celecoxib was associated with a lower incidence of symptomatic ulcers and ulcer complications combined compared with NSAIDs at standard dosages.⁷ Laine et al. found that rofecoxib administration, at doses 2-4 times the dose demonstrated to relieve symptoms of osteoarthritis, caused significantly less gastroduodenal ulceration than ibuprofen, with ulcer rates comparable to placebo.⁸

COX-2 inhibitors appear to exert less of an antiplatelet effect than is commonly seen by traditional NSAIDs. In several Phase II clinical studies, celecoxib, in therapeutic to high-therapeutic doses, was not associated with any clinically meaningful changes in platelet aggregation. These findings were in contrast to significant decreases in platelet aggregation reported with standard doses of traditional NSAIDs.^{9,10} Leese et al. also found that while the traditional NSAIDs, ibuprofen and naproxen, caused significant reductions in platelet aggregation, celecoxib demonstrated a minimal effect on platelets.¹¹

Although traditional NSAIDs have been well documented as causing decreased renal perfusion, increased GI irritation, and decreased platelet aggregation, in an otherwise healthy, compliant patients, COX-2 selective inhibitors do not offer enough of an advantage to warrant their use. The only advantages that appear to be clinically relevant are the decreased GI irritation and decreased platelet interference. Thus COX-2 selective inhibitors would arguably offer an advantage only in those patients with an increased risk for GI ulceration or those on stable anticoagulation regimens.

Despite the inviting sound of treatment with a NSAID without side effects, it appears that the COX-2 selective

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Table I: Drug-Herb Interactions of Commonly Prescribed Drugs⁴

Rx Drug	Herb	Interaction
Benzodiazepines	Kava kava	Excessive sedation
Corticosteroids	Echinacea, astragal, licorice, alfalfa sprouts, Vit E, and Zinc	May offset immunosuppressive effects of corticosteroids
Digoxin	Cardiac glycoside containing herbs, licorice, hawthorne, uzara root	May have additive effect
Diuretics	Sodium sparing herbal aquaretics (dandelion, uva-ursi)	May offset antihypertensive effects of HCTZ & furosemide
Hypoglycemic	Chromium	May decrease insulin requirements
Levothyroxine	Horseradish and kelp	May suppress thyroid function
NSAIDs	Gossypol, uva-ursi	Increased GI irritation with some herbs
Phenelzine & other MAO-inhibitors	Ginseng, yohimbine, Ephedra, St John's wort	May cause insomnia & headache; St John's wort --possibility of serotonin syndrome
Phenytoin	Wormwood, sage, evening primrose oil, borage, shankhapulshpi	May shorten half-life of phenytoin
Warfarin	Garlic, ginger, ginkgo, feverfew, ginseng	May increase anticoagulant effects; ginseng may decrease effectiveness

New Drug Facts: NEXIUM® (ESOMEPRAZOLE)

Another new drug has hit the market. However, this drug is very similar to one that is already available. In fact, they are even marketed by the same drug company. It is a case of racemic mixtures (omeprazole) versus active isomers (esomeprazole).

Esomeprazole (Nexium®) is the newest drug in a class of medications known as proton-pump inhibitors. It is an isolated formulation of the S-isomer of omeprazole (Prilosec®). Esomeprazole is indicated for use in gastroesophageal reflux disease (GERD) and in combination with amoxicillin and clarithromycin (triple therapy) for eradication of *H. pylori* associated ulcer disease and reduction of the risk of ulcer recurrence. Just as the other approved proton-pump inhibitors, esomeprazole suppresses gastric acid secretion through inhibition of the H⁺/K⁺-ATP-ase pump in the parietal cell, blocking the final step in acid production.

Esomeprazole is currently available in two different strengths: 20-mg and 40-mg capsules containing enteric-coated pellets. The pharmacology and pharmacokinetics of esomeprazole are similar to that of the other proton-pump inhibitors. The half-life is approximately 1.5 hours, but the duration of action is 24 hours, allowing for once-daily dosing. Esomeprazole is metabolized through the cytochrome P450 system and therefore has the potential to interact with other medication metabolized through this pathway. Although phenytoin, warfarin, and quinidine are metabolized through these pathways, there are no documented interactions between these drugs and esomeprazole. However, concomitant use of diazepam may result in an

increase in the concentration of diazepam. Also, absorption of medications that require an acidic environment may be compromised with concomitant use of esomeprazole.

Safety data comparing esomeprazole to placebo and omeprazole have demonstrated tolerability of esomeprazole in short and long term studies. The most commonly reported side effects were headache and diarrhea. Other side effects reported (e.g., abdominal pain, constipation, dry mouth, flatulence, and nausea) were similar in rate of occurrence to those observed with omeprazole. Side effects that were

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reported in less than one percent of patients were considered rare and include: allergic reactions, anemias, arthralgias, edema, hypertension, increase in liver function tests, and sleep disturbances.

The majority of efficacy studies compare 40-mg of esomeprazole to 20 mg of omeprazole. One study revealed that esomeprazole 40 mg was significantly superior to omeprazole 20 mg in resolution of heartburn, percent free heartburn days and nights, and in endoscopy confirmed healing of reflux esophagitis. However, the doses used for the comparisons are not equivalent. Prilosec® consists of a racemic mixture of omeprazole (50% S-

isomer and 50% R-isomer), where esomeprazole is 100% S-isomer of omeprazole, the most active isomer of the two. A 20-mg capsule of esomeprazole contains the same amount of active ingredient found in a 40-mg capsule of omeprazole. Therefore, a 40 mg dose of esomeprazole would be comparable to an 80 mg dose of omeprazole instead of the 20 mg dose of omeprazole used in clinical trial comparisons. There are no equivalent comparisons available to adequately compare esomeprazole to omeprazole.

In conclusion, esomeprazole appears to be safe and effective in the treatment of GERD. However, the dosages used to compare efficacy with omeprazole in clinical trials should not be used to state that esomeprazole is more effective than omeprazole. At this time, there is no strong evidence to support selection of esomeprazole over omeprazole. The only advantage of selecting esomeprazole over omeprazole is a slight decrease in monthly cost for patients without prescription insurance coverage. However, this advantage will soon disappear when generic forms of omeprazole become available.

By Lisa Bradshaw, Pharm.D.

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2. Racemic Switching. *C&E News*. 2000;78(4):55-78
3. Esomeprazole® package insert

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inhibitors are not the ultimate answer for pain and inflammation control. The difference in the cost of one year's therapy is hundreds of dollars more expensive for COX-2 selective regimens. Celecoxib is indicated for use in osteoarthritis, rheumatoid arthritis and familial adenomatous polyposis. Rofecoxib is indicated for use in osteoarthritis, acute pain and primary dysmenorrhea. However, considering the

data currently available in the literature, the use of COX-2 inhibitors should be restricted to patients with these conditions who are on anticoagulation therapy, elderly, unable to tolerate the GI effects of traditional NSAIDs, or have an increased risk for GI ulceration. Due to their prohibitive cost and similar side effect profile, these agents should rarely be used in lieu

of traditional NSAIDs in the majority of patients.

By Brian Sweat, Pharm.D.

References available upon request.

<http://pharmacy.auburn.edu/dilrc/index.html>

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FDA Update**SAFETY WARNINGS****Itraconazole (Sporanox®)**

The FDA recently released updated labeling information regarding the safety of itraconazole products in the treatment of fungal nail infections. Recent research indicates a small risk of developing congestive heart failure (CHF) with use of itraconazole. Post-marketing adverse event reports reveal 94 cases of CHF in patients taking itraconazole. The FDA suspects that 58 of these cases were due to administration of itraconazole. The "black box" warning on itraconazole has been updated to recommend avoidance of use in patients with evidence of cardiac dysfunction, including CHF or history thereof, and discontinuation of the agent if signs and symptoms of CHF occur during treatment of fungal nail infections.¹

Itraconazole (Sporanox®) and Terbinafine (Lamisil®)

Although the labeling of itraconazole products and terbinafine tablets already include a warning of adverse liver effects, recent numbers of case reports with both medications have prompted the FDA to revisit the issue. As of March and April of this year, 16 possible terbinafine-associated and 24 possible itraconazole-associated cases of liver failure have been reported; twenty-two cases resulted in death. Due to this serious risk, the FDA has updated the labeling of these agents. The new labeling recommends obtaining nail specimens for evaluation prior to initiating treatment with either agent.¹

DOSAGE ADJUSTMENT Famotidine (Pepcid®)

Recent reports of central nervous system adverse events in patients with moderate to severe renal dysfunction have resulted in new labeling for famotidine. Previous labeling recommended dosage adjustment in patients with severe renal insufficiency (CrCl <10ml/min). New labeling recommends a 50% dose reduction or extension of the dosing interval to 36 to 48 hours in patients with moderate (CrCl <50ml/min) and severe renal insufficiency.²

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