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Hope for the Calorically Challenged

ABSTRACT & COMMENTARY

Synopsis: *A 10% change in weight has a significant effect on the severity of sleep-disordered breathing.*

Source: Peppard PE, et al. *JAMA* 2000;284:3015-3021.

This is a prospective, population-based study of 690 wisconsonites. Their mean age at entry was 46 years, and 56% were men. Body mass index (BMI, kg/m^2) and apnea plus hypopnea index (AHI) were measured at baseline and four years later. At baseline and follow-up, AHI was correlated with BMI. At baseline, the 181 normal weight (BMI < 25 kg/m^2) group had an AHI of 1.2 (± 2.4 events/h) The 241 overweight (25 < BMI < 30 kg/m^2) subjects had an AHI of 2.6 (± 4.5 events/h). The 268 obese (BMI > 30) individuals had an AHI of 7.4 (± 13.1) events per hour. In follow-up, change in AHI was related to change in weight in a dose-response fashion. Thirty-nine subjects developed moderate-to-severe sleep apnea over the four years of study; this group had a mean weight gain of 3.9 (± 6.8) kg. Seventeen individuals who had moderate-to-severe sleep apnea at baseline had a reduction in AHI to below 15 events per hour at follow-up; this group lost 3.1 (± 6.2) kg. Each percentage change in weight (in either direction) was associated with an approximately 3% change in the AHI. Adjustment for menopausal status, physical activity, alcohol, or educational level did not materially affect the relationship between weight change and AHI. Cigarette smoking status was associated with change in AHI because smoking cessation was associated with weight gain in this study. However, change in cigarette packs smoked per week did not change the relationship between AHI and BMI.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

A history of recent weight gain is a common presenting symptom in patients with newly diagnosed sleep apnea. This study helps us to understand why. A 200-pound man who has an AHI of 12 would be predicted to have an AHI of about 15 or 16 if he gains 20 pounds. Although the exact AHI necessary to be clinically significant varies

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from person to person, most people with an AHI of 15 will be symptomatic. There is both good news and bad news here: the good news is that just a little more than 3 kg weight loss essentially cured some sleep apneics in this study. The bad news is that just a little more than 3 kg weight gain tipped some patients over into sleep apnea territory. And, in this study (as in my clinical practice, alas), there were far more people who gained weight than who lost it.

BMI has long been known to be associated with overall mortality. In healthy people who have never smoked, death from all causes rises progressively above a BMI of 23.5-24.9 in men and 22.0-23.4 in women.[1] Much of the excess mortality associated with obesity is due to cardiovascular disease. Obstructive sleep apnea has been conclusively linked to hypertension and its sequelae,[2-6] even controlling for obesity. Sleep-disordered breathing is part of the causal link between obesity and death.

One caveat to this important study is that the relationship between obesity and the risk of sleep apnea may not be so straightforward in non-Caucasian people. Several recent studies have demonstrated that ethnicity, particularly Asian and African-American race, are important risk factors for sleep apnea independent of obesity.[7-12] (*For a user-friendly website to calculate BMI, see: http://healthlink.mcw.edu/article/923520512.html.*) ❖

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The Use of Lipid-Lowering Drugs for Primary Prevention of Coronary Heart Disease

ABSTRACT & COMMENTARY

Synopsis: *Primary prevention using statin drugs reduces the incidence of coronary heart disease events but not all-cause mortality.*

Source: Pignone M, et al. *BMJ* 2000;321:983-986.

The effectiveness of drug treatment for lipid disorders in patients with no history of coronary heart disease (CHD) has been controversial. Pignone and colleagues point out that a recent review of lipid-lowering treatment with statins found that CHD events and all-cause mortality were decreased in primary prevention populations.[1] Also, new data from the large Air Force/Texas coronary artery prevention study, which examined women and men with poor ratios of total cholesterol (TC) to high-density cholesterol (HDL) and modest risk (0.5-1%), found that lovastatin reduced the

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risk of the first major coronary event.[2]

Pignone et al searched the Medline database from January 1994 to June 1999 for English language studies examining drug treatment for lipid disorders. The inclusion criteria were all randomized trials of at least one year's duration that examined drug treatment for patients with no known CHD, cerebral vascular disease, or peripheral vascular disease, and measured all-cause mortality, CHD mortality, and nonfatal myocardial infarction.

Four studies met the criteria. Drug treatment reduced the odds of a CHD event by 30%, but not the odds of all-cause mortality. When statin drugs were considered alone, no substantial differences in the results were observed.

They concluded that treatment with lipid-lowering drugs lasting 5-7 years reduces CHD events but not all-cause mortality.

COMMENT BY RALPH R. HALL, MD, FACP

These studies are interesting for a number of reasons. The Airforce/Texas study supports the inclusion of HDL in the risk factor assessment by the National Cholesterol Education Program guidelines. A number of investigators have advocated the inclusion of HDL for some time. Also, all-cause mortality was not increased as it has been in some studies.

The long-term use of these drugs, as well as the use of fibrates, which have also been successful in patients with low HDL levels, is still of some concern.

Newspapers throughout the country have reported that the Food and Drug Administration rejected proposals by the manufacturers of lovastatin and pravastatin to make these drugs available over the counter.

As noted by Hulley and colleagues in an editorial, the arguments for allowing over-the-counter sales were that statins are effective, easy to take, relatively safe, and many people who should take the drugs are not doing so.[3]

The underuse of statins is most apparent in secondary prevention of patients with known heart disease. Only about one-third of the patients with elevated lipids are treated after they have had a myocardial infarction and many of those treated are not treated until the recommended goals for lipid lowering have been attained.

One note of caution is indicated for physicians who recommend long-term therapy with the statins—the potential for tachyphylaxis. A recent study of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin demonstrated that LDL tachyphylaxis appeared to be a unique response to prolonged use of atorvastatin at the doses usually given.[4] ❖

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Soy Protein and Hot Flashes

ABSTRACT & COMMENTARY

Synopsis: *A double-blind, placebo-controlled trial of a relatively large dose of soy supplements could detect no effect on menopausal symptoms.*

Source: Kotsopoulos D, et al. *Climacteric* 2000;3:161-167.

Kotsopoulos and colleagues from the monash Medical Centre in Australia randomized 97 postmenopausal women 50-75 years of age to soy supplements or placebo in a double-blind trial. The dose of isoflavones in the soy supplement given daily for three months was 118 mg. These women were experiencing a relatively high frequency of menopausal symptoms at baseline, although the severity was not extreme. The intake of soy protein was confirmed by demonstrating an increase in the urinary excretion of genistein and daidzein. No effect compared with placebo could be detected in vaginal dryness, libido, vasomotor reactions (hot flushes), psychological symptoms, or musculoskeletal complaints.

COMMENT BY LEON SPEROFF, MD

Phytoestrogens is a descriptive term applied to nonsteroidal compounds that have estrogenic activity or are metabolized into compounds with estrogen activity. Phytoestrogens are classified into three groups: isoflavones, coumestans, and lignans. Soybeans are a rich source of phytoestrogens, containing the most common form of phytoestrogens, the isoflavones (mainly genistein and daidzein, and a little glycitein). Isoflavones exist in plants bound as glycoside conjugates attached at the 3 position, called glycones. The carbohydrate component requires gut bacteria to remove the sugar moiety to produce active compounds, the aglycones. Individual variability in gastrointestinal microflora, as well as absorption, influences the bioavailability of isoflavones.

You can eat soybeans every day and never see a bean. Soy flour is prepared to remove the carbohydrates. Ninety-five percent of soy flour is toasted and used as animal feed. Alcohol washing is used to get a taste-free

product, but alcohol extraction removes the phytoestrogens. SUPRO from Protein Technologies International does not use alcohol extraction. SOYSELECT (Indena, Milan, Italy) and HEALTHY WOMEN (Johnson and Johnson, United States) are alcohol extracts. Oil and margarine have only traces of isoflavones; the conjugates are not soluble in oil.

The average Japanese intake of isoflavones is about 50 mg/d. Previous numbers were higher and were overestimated. The rest of Asia is about 25-45 mg/d, and Western consumption is less than 5 mg/d. A belief that Asian women report fewer menopausal symptoms is an underlying driving force in the promotion of isoflavones. However, this apparent difference in the prevalence of symptoms comparing Asia and the West may reflect cultural differences, not actual experience. It is important to keep in mind that the Cochrane Collaboration review of controlled trials found an average 51% reduction in hot flush frequency with placebo treatments. Therefore, studies of flushing without randomization to placebo treatment are not helpful.

An Italian study using SUPRO found a 45% reduction in flashing with 60 g of isolated soy protein daily (76 mg isoflavones), compared with a 30% reduction in the placebo group.[1] Two other studies, both with 50 mg/d of isoflavones, found a similar 15% reduction in the number of flashes compared with placebo.[2,3] In a randomized, crossover study of a high dose of isoflavones for flashes in breast cancer survivors, there was no effect.[4] The dose was 150 mg isoflavones per day, similar to three glasses of soy milk daily. Why do these studies differ? It is unlikely to be a difference in dosing, in that the doses studied have ranged from 50 mg to 150 mg of isoflavones per day (the latter being a rather high dose). Perhaps the 15% difference compared with placebo observed in two studies reflects an effect on severe hot flushing, while mild-to-moderate hot flushing is not affected. However, a 15% difference is slight, and I suspect that clinicians would find it hard to observe this difference in an individual practice.

PROMENSIL is an extract of red clover (*Trifolium pratense*) containing formononetin, daidzein, biochanin, and genistein. Formononetin and biochanin are metabolized to daidzein and genistein, respectively. Red clover is a legume used to enrich nitrogen levels in soils. Promensil is produced by Novogen in Australia and marketed by Solvay in the United States. A 500 mg tablet contains 200-230 mg of dried aqueous-alcoholic extract, which contains 40 mg of isoflavones. The recommended dose is one tablet daily.

Two randomized, placebo-controlled studies of the effect of Promensil on hot flushes were reported in 1999, in *Climacteric*, the journal of the International Menopause Society.[5,6] Neither demonstrated a significant difference compared with the placebo group. In one of the reports, four times the recommended dose (4 tablets daily) also had no effect.

I believe there is now sufficient evidence of appropriate quality to allow us to tell our patients that soy protein and isoflavone supplements do not help hot flushing. Any effect a patient experiences is a placebo response, not to be underrated, but certainly to be understood by the clinician and patient. In my opinion, there is only one medicine. Anything claiming to treat or prevent health problems must withstand the rigor of scientific studies of efficacy and safety. Anything with the potential to affect health must be subject to this requirement. The simplicity and correctness of this argument are so overwhelming, I believe it will come to be so. (*Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland, Ore.*) ❖

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Even Moderate Obesity is Associated with Thromboembolism After Total Hip Arthroplasty

ABSTRACT & COMMENTARY

Synopsis: *A body mass index of 25 or greater was associated with subsequent hospitalization for thromboembolism in patients undergoing total hip arthroplasty.*

Source: White RH, et al. *N Engl J Med* 2000;343:1758-1764.

The three-month incidence of symptomatic thromboembolism after total hip arthroplasty is approximately 3-4%, according to White and colleagues. More than 75% of these events are diagnosed after the patient is discharged from the hospital.[1] They noted that the risk factors associated with these events are not well defined.

Using administrative data from the California Medicare records for 1993 through 1996, they identified 297 patients 65 years or older who were rehospitalized for thromboembolism within three months after total hip arthroplasty. They compared demographic, surgical, and medical variables in these patients with 592 unmatched controls.

A total of 89.6% of the patients with thromboembolism and 93.8% of control patients were treated with pneumatic compression, warfarin, enoxaparin, or unfractionated heparin alone or in combination. In addition, 22.2% and 29.7%, respectively, received warfarin after discharge.

White et al concluded that a body mass index (BMI) of 25 or greater was associated with rehospitalization for thromboembolism, with an odds ratio of 2.5. The only prophylactic regimens associated with a reduced risk of thromboembolism were pneumatic compression in patients with a BMI of less than 25 (odds ratio, 0.3) and warfarin treatment after discharge (odds ratio, 0.6).

COMMENT BY RALPH R. HALL, MD, FACP

The last 10-15 years have seen significant improvement in the methods for the management of patients with the potential for thromboembolism. Advanced age, previous deep venous thrombosis, immobility, and the presence of genetic or acquired risk factors, such as antithrombin, protein C abnormalities, protein S deficiencies, factor V Leiden, hyperhomocysteinemia, and others have been recognized as precipitating factors.

There are numerous instances, however, in which none of these factors are present. Obesity and leg varicosities have been suspected causes, but their association with thromboembolism has not been well documented.

Also noted in this study's results was that ambulation before day 2 after surgery had a protective effect. How important is mobility after the patient is discharged? How active or inactive were these patients after discharge? What other factors may associated with obesity?

Many of the laboratory tests for clotting abnormalities are expensive and complicated and, therefore, have not gained acceptance in clinical practice. Therefore, as White et al point out, we must improve our efforts to focus on improving the effectiveness of in-hospital as well as postdischarge thromboprophylaxis in overweight patients. ❖

Reference

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Nitric Oxide as a 'NOvel' Therapy for Gastrointestinal Ulcers?

ABSTRACT & COMMENTARY

Synopsis: *Drugs that release nitric oxide have been shown to prevent ulcers and accelerate ulcer healing in animals. This large, case-control study demonstrates that oral or transdermal nitrosovasodilators are independently associated with a reduced risk of upper gastrointestinal bleeding.*

Source: Lanas A, et al. *N Engl J Med* 2000;343:834-839.

Lanas and colleagues studied the relationship between medications that release nitric oxide (oral or transdermal preparations of nitroglycerin), medications that promote ulcers (low-dose aspirin, high-dose aspirin, and other nonsteroidal anti-inflammatory drugs [NSAIDS]), anti-acid agents (H_2 receptor antagonists and omeprazole), and the risk for developing upper gastrointestinal (GI) bleeding. They performed a case-control study of 1122 consecutive patients admitted with upper GI bleeding to one of four general hospitals in Spain. The 2231-patient control group consisted of 1109 patients hospitalized for other reasons and 1122 outpatients from the same region. Control subjects were chosen to achieve frequency matching with the patients according to sex and age.

As expected, the use of NSAIDS was associated with an increased risk of bleeding (odds ratio, 7.4 for NSAIDS other than low-dose aspirin and 2.4 for low-dose aspirin), and anti-secretory therapy was protective (odds ratio, 0.6). Omeprazole, a proton-pump inhibitor, was more effective than H_2-receptor antagonists. Interestingly, the use of nitrosovasodilators was protective as well, with an odds ratio of 0.6 and a 95% confidence interval of 0.4-0.8. Despite the antiplatelet effects of nitric oxide, nitrosovasodilators appeared to prevent GI bleeding.

COMMENT BY MARK T. GLADWIN, MD

Nitric oxide is a free-radical gas molecule produced endogenously by the nitric oxide synthase enzyme systems, and plays a critical role in the regulation of blood flow, immune function, and cellular signal transduction. Recent data suggest that nitric oxide increases gastric mucosal blood flow and inhibits leukocyte adherence to the GI microvasculature. These properties

result in reduction in ulcerogenesis and improvement in ulcer healing in rats treated with oral or intravenous nitroglycerin. A nitric oxide-releasing aspirin product has even been developed to reduce ulcer formation. Critically ill patients are highly susceptible to gastric and duodenal erosion, ulceration, and bleeding, particularly in the presence of coagulopathy and the need for mechanical ventilation. While antisecretory therapies are protective, they increase the risk of nosocomial pneumonia, and breakthrough bleeding is common. For these reasons, new therapies to reduce the incidence of GI bleeding in the ICU are needed. These data suggest that nitric oxide releasing compounds, taken orally or transdermally—and, thus, suggesting that intravenous therapy would be effective—reduce the clinical risk of GI hemorrhage. Studies in ICU patients at risk for such bleeding should be undertaken in order to determine whether nitroglycerin preparations should be administered daily, enterally or transdermally, to mechanically ventilated ICU patients. Will these therapies be effective in this population and will they demonstrate additive or synergistic effects with antisecretory therapy? (*Dr. Gladwin is Senior Research Fellow, Department of Critical Care Medicine, National Institutes of Health, Bethesda, Md.*) ❖

Pharmacology Update

Lansoprazole Capsules: A New Indication

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Lansoprazole has been granted a new indication by the FDA—it is the first proton pump inhibitor (PPI) approved for the treatment of NSAID-associated gastric ulcers. The drug was introduced in 1995 and marketed as Prevacid by TAP Pharmaceuticals.

Indications

Lansoprazole has gained FDA approval for the healing of NSAID-associated gastric ulcer in patients who continue NSAID use and for the risk reduction of NSAID-associated gastric ulcer with history of a documented gastric ulcer who require the use of a NSAID.

Dosage

For the healing of NSAID-associated gastric ulcer, the recommended dose is 30 mg once daily for eight weeks. For the risk reduction of NSAID-associated gastric ulcer, the recommended dose is 15 mg once daily for up to 12 weeks.[1]

Lansoprazole is available as 15 mg and 30 mg capsules.

Potential Advantages

Lansoprazole is the first PPI approved for NSAID-associated gastric ulcer treatment in patients continuing NSAID therapy. Lansoprazole is more conveniently dosed once daily compared to 2-4 times a day dosing of misoprostol. The latter is FDA approved for the prevention of NSAID-induced gastric ulcers in patients at high risk of complication from gastric ulcers.

Potential Disadvantages

Lansoprazole (15 mg or 30 mg) is reported to be less effective than misoprostol in reducing the risk of NSAID-associated gastric ulcer.[1] After 12 weeks of treatment, the percentages of patients remaining gastric ulcer free were 80%, 82%, and 92%, respectively, for lansoprazole 15 mg daily, lansoprazole 30 mg daily, and misoprostol 200 mcg four times daily.

Comments

PPIs are important agents for the treatment and prevention of NSAID-associated gastric and duodenal injury. Omeprazole, the first PPI marketed, is more efficacious than ranitidine in healing and preventing NSAID-associated gastroduodenal ulcers.[2,3] Similarly, lansoprazole has been shown to be more effective than ranitidine in healing NSAID-associated gastric ulcers.[4] Lansoprazole appears to be less effective than misoprostol (200 mcg 4 times a day) in preventing NSAID-associated gastric ulcer.[1] Omeprazole has been reported to be comparable to a lower dose of misoprostol (200 mcg twice daily) in preventing gastric ulcers.[5] Misoprostol, however, is generally not well tolerated due to diarrhea and abdominal pain, may be less effective in preventing duodenal ulcers, and requires multiple daily dosing.[5] Lansoprazole is currently the only PPI approved for treatment of NSAID-associated gastric ulcers in patients continuing NSAID therapy. However, it is reasonable to believe that omeprazole is equally effective.

Clinical Implications

Studies have indicated that the attributable risk of ulcer complications for NSAID users is 25-35%.[6] It was estimated that there are more than 100,000 annual hospitalizations for serious gastrointestinal (GI) complications due to NSAID use.[2] Risk factors include age, male

gender, past history of peptic ulcer disease, NSAID dose, and the use of corticosteroids or anticoagulants.[6,7] For patients who need to continue NSAID therapy, a PPI is effective in healing gastric and duodenal ulcer in *H. pylori*-positive or -negative patients.[2,6] For primary or secondary prophylaxis, concomitant treatment with a PPI or misoprostol are reasonable choices. Selective cyclooxygenase inhibitors, such as celecoxib or rofecoxib, may provide another alternative, although their role in patients with active GI disease has not been adequately studied as these were generally excluded in published studies.[8,9] These patients may still require concomitant therapy with a PPI.[6,10] ❖

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CME Questions

6. The relationship between body mass index (BMI) and apnea plus hypopnea index is which one of the following?

a. Each percentage change in BMI is associated with a 1% change in AHI.
b. Each percentage change in BMI is associated with a 3% change in AHI.
c. Each percentage change in BMI is associated with a 5% change in AHI.
d. Each percentage change in BMI is associated with a 10% change in AHI.
e. Each percentage change in BMI is associated with a 20% change in AHI.

7. Which one of the following statements is *not* true?

a. Some studies have reported an increase in all-cause mortality in patients treated with lipid-lowering drugs.
b. The Airforce/Texas Heart study points out the benefits of treating patients without a previous coronary event who have low levels of HDL cholesterol.
c. Tachyphylaxis is a problem with all statins.
d. A high percentage of patients who should be treated with lipid-lowering drugs are not treated.

8. Which of the following statements is true?

a. Administration of inhaled nitric oxide prevents ulcer formation in critically ill patients.
b. Nitroglycerin therapy is associated with a reduced risk of gastrointestinal bleeding in hospitalized patients.
c. Patients receiving both nitroglycerin and omeprazole have an increased incidence of upper gastrointestinal bleeding.
d. Omeprazole releases nitric oxide into the gastric lumen.
e. H_2 blockers such as ranitidine and cimetidine release nitric oxide into the gastric lumen.

9. The following statements are true regarding soy protein and menopausal symptoms *except*:

a. The placebo response is so powerful that any study of menopausal symptoms requires a double-blind, placebo-controlled design.
b. Supplementation of the diet with soy protein may have a slight effect on very severe hot flushing.
c. Supplementation of the diet with soy protein may have an effect on the frequency of hot flushing.
d. Increasing the dose of isoflavones in soy protein supplements will not produce a better effect on hot flushing.

10. Lansoprazole capsules:

a. have been granted a new indication for treating NSAID-associated gastric ulcers.
b. is the first PPI approved for NSAID-associated gastric ulcer treatment in patients continuing NSAID therapy.
c. are dosed once daily.
d. are reported to be less effective than misoprostol in reducing the risk of NSAID-associated gastric ulcer.
e. All of the above

By Louis Kuritzky, MD

Prevention of Hip Fracture in Elderly People with Use of a Hip Protector

Despite enhanced pharmacologic therapies for osteoporosis prevention and treatment, hip fractures remain an important individual and public health problem. Since the mean age of the population continues to increase, it is likely that management of hip fracture will become even more pertinent. In this study, Kannus and associates report on the use of a hip protector (specifically, KPY Hip Protector, Respecta, Helsinki, Finland) worn to reduce the effect of trauma upon the hip. Each patient in the treatment group (n = 653) wore bilateral 19 cm conical padded hip protectors daily.

During the study period, compliance with the device was a modest 48% (i.e., treatment group participants actually wore the devices only half the days). Nonetheless, almost three-quarters of the falls that occurred in this group happened while wearing protectors. There were 13 treatment group patients who had a hip fracture vs. 67 control subjects (relative hazard = 0.4). Similarly, the pelvic fracture rate was halved by use of the hip protector, despite the fact that some fractures occurred in the treatment group while they were not wearing their protectors. Adverse reactions attributable to wearing the protectors were few and generally inconsequential. Protective padding, for those willing to use it, offers an effective preventive for hip fracture. ❖

Kannus P, et al. N Engl J Med 2000; 343:1506-1513.

The Effect of Fecal Occult-Blood Screening on the Incidence of Colorectal Cancer

As demonstrated by both randomized and observational studies, the mortality rate of colorectal cancer (CRC) is reduced by fecal occult blood testing (FOBT). The favorable effect of FOBT upon CRC mortality has been attributed to earlier stage of tumor at time of detection, surgical excision of tumors, and removal of premalignant lesions. This report details the results at 18 years of follow-up for participants in the Minnesota Colon Cancer Control Study (n = 46,551), which used annual, biennial, or "usual care" for FOBT screening. Persons with any positive FOBT were offered colonoscopy.

The cumulative incidence of CRC in both screening groups was significantly (17-20%) less than in the control group. Mandell and colleagues challenge the theory suggested by others that mortality reduction is a consequence of chance tumor detection at colonoscopy; they suggest that it is the sensitivity of FOBT testing that is responsible for the improved outcome. No significant difference was found between yearly vs. every two years of FOBT screening. ❖

Mandell JS, et al. N Engl J Med 2000; 343:1603-1607.

Short-term Prognosis After Emergency Department Diagnosis of TIA

Short-term outcome after transient ischemic attack (TIA) has been a topic investigated in only a few settings. Confirmation of TIA diagnosis may be contentious, since seizure, syncope, migraine, and other etiologies can be mistaken for TIA. This study evaluated persons presenting to emergency departments (EDs) in a single health maintenance organization over one year with a diagnosis of TIA (n = 1707).

Within 90 days after presentation to the ED, 10.5% of patients suffered a completed stroke. Although TIA patients who received anticoagulation at discharge from the ED were subsequently more likely to suffer a completed stroke, it has been suggested that perhaps those individuals were perceived to have been at greater stroke risk at the time of ED presentation. A favorable trend toward stroke reduction was seen in antiplatelet recipients (e.g., aspirin, ticlopidine). Five items were determined to be independent risk factors for stroke within 90 days: age older than 60, diabetes, TIA enduring over 10 minutes, weakness with TIA, and speech impairment with TIA. ❖

Johnston SC, et al. JAMA 2000;284: 2901-2906.

In Future Issues: Preclinical Alzheimer's Disease

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Herb-Drug Interactions: An Evidence-Based Table

By Mary L. Hardy, MD

As patients' use of herbal products increases, so do physicians' concerns regarding the possibility of herb-drug interactions. Uncertainty in this area is rife (e.g., active constituents, mechanisms of action, consistency of products) and complicates the assessment of available data. Current literature consists mainly of case reports that often are not adequately investigated. There are few clinical trials and the pharmacologic data available have not been assessed for clinical relevance.

Further, patients have been reluctant to disclose fully their use of natural products to their physicians, so interactions generally only come to light when a serious problem occurs. Most doctors, without adequate training in this area, feel uncomfortable commenting on or even reporting cases that involve the use of herbal medications. Too much of our experience is theoretical or anecdotal.

For commonly used herbs and commonly prescribed drugs, I have assembled a detailed compendium of herb-drug interactions. This table is designed to provide clinicians with guidance in assessing the potential for interaction. It cites a mechanism for interaction where one is known or postulated. It reports the level of evidence for that interaction. It also offers a clinically useful scale for the evidence, outlined in Table 1.

The drug-herb interaction table is not exhaustive and should be considered a work in progress. New data will become available, and as we learn more about which herbs interact with which drugs, we will report significant findings in future newsletters. A limited bibliography is available on request. ❖

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Table 1

Level of evidence to support use

CT = Controlled trial	CS = Case series
CR = Case report	AS = Animal study
TU = Traditional use	P = Pharmacology
TH = Theoretical	

Table 2

Herb-Drug Interactions

Drug Category	Herbs	Herb Effect	Mechanism (Evidence Type)
Alkaloids	High tannin-containing (e.g., caffeine-containing herbs, cat's claw, tea, uva ursi)	Decreased plasma levels	Precipitation of alkaloids by tannins (TU)
Anesthetics	Kava, valerian	Prolongation of sedation time	Additive effect (CR)
Antihypertensives	a. Licorice b. Sympathomimetic herbs (e.g., ephedra)	Decreased therapeutic effect	a. Increased salt and water retention (CR) b. Opposition of therapeutic action (P)
Antiarrhythmics	Cathartic laxatives (e.g., aloe, cascara, senna, yellow dock), diuretics (e.g., celery seed, corn silk, horsetail, juniper), licorice	Increased side effects (arrhythmia)	Increased potassium loss (P)
Antiarrhythmics	Anticholinergic herbs (not generally used clinically, e.g., belladonna)	Decreased therapeutic effect	Decreased absorption (P, TH)
Anticoagulants	Antiplatelet-aggregating (e.g., *Panax ginseng*, feverfew, garlic, ginkgo)	Increased side effect (bleeding)	Inhibition of platelet aggregation through inhibition of thromboxane synthetase (ginger) (P); arachadonic acid production (feverfew) (P); inhibition of epinephrine induced in vitro (garlic) (P); platelet thromboxane synthetase aggregation (garlic) (P, CR); inhibition of platelet activating factor (ginkgo) (CR)
Anticoagulants: Warfarin	*Panax ginseng*, St. John's wort	Opposition of therapeutic effect; decreased enzyme bioavailability	Unknown (CR); hepatic induction (CS)
Anticoagulants: Warfarin	Coumarin-rich herbs, (e.g., sweet clover, danshen), white clover	Increased therapeutic effect	Only danshen has been observed to do this clinically. Increased maximum concentration and decreased volume of distribution (CR, P)
Anticoagulants: Warfarin	Vitamin K-rich herbs (e.g., collard, kale, spinach)	Decreased therapeutic effect	Opposes activity (CR, P)
Anticonvulsants	a. GLA-rich herbs b. Thujone-containing herbs (e.g., cedar, tansy, sage)	Decreased therapeutic effect	GLA (CR) and thujone may decrease seizure threshold; mechanism unknown

Drug Category	Herbs	Herb Effect	Mechanism (Evidence Type)
Anticonvulsants	Salicylate-rich herbs (e.g., cramp bark, willow, wintergreen)	Increased therapeutic effect	Transient; unknown mechanism (CR)
Anticonvulsants: Phenytoin	Shankapulshpi (Ayurvedic preparation with multiple herbs)	Opposition of therapeutic action	Decreased effectiveness of drug; decreased drug levels (CR)
Antiplatelet-aggregating	Antiplatelet-aggregating (e.g., *Panax ginseng*, feverfew, garlic, ginkgo)	Increased side effect (bleeding)	Similar therapeutic action (P, CR)
Barbiturates	Valerian	Increased therapeutic effect; increased side effects	Shown to prolong barbiturate-induced sleep (AS)
Benzodiazepines	St. John's wort, kava	Decreased therapeutic efficacy; may increase side effects; increased sedation	Herb binds to GABA receptor site (AS, P)
Cardiac glycosides	Cardiac glycoside-containing herbs (e.g., foxglove, lily of the valley)	a. Enhanced therapeutic effect b. Increased side effects (arrhythmia)	Same active constituents (TH)
Cardiac glycosides	Cathartic laxative herbs (e.g., aloe, cascara, senna, yellow dock), licorice, diuretic herbs (e.g., celery seed, corn silk, horsetail, juniper)	Increased side effects (arrhythmia)	Increased potassium loss (TH)
Cardiac glycosides	Quinine-containing herb (e.g., cinchona bark)	Increased plasma levels	(TH)
Cholesterol-lowering drugs	Garlic, artichoke, ginger, fenugreek	Increased therapeutic effect	Similar clinical effect via different mechanism (TH)
Corticosteroids	Cathartic laxative herbs (e.g., aloe, cascara, senna, yellow dock), diuretic herbs (e.g., celery seed, corn silk, horsetail, juniper)	Increased side effects	Both cause increased potassium loss (TH)
Corticosteroids	Licorice	Increased plasma levels	Increased half-life (increased bioavailability) (CR); inhibition of ll-ß-dehydrogenase (P)
Corticosteroids	*Panax ginseng*	Increased side effects	Similar side effects of CNS stimulation and insomnia (CR)
Digoxin	Siberian ginseng	Increased plasma level	Mechanism unknown; validated by rechallenge (CR)

Drug Category	Herbs	Herb Effect	Mechanism (Evidence Type)
Digoxin	a. Kyushin (Chinese remedy containing the venom of the Chinese toad) b. *Panax ginseng*	Increased serum levels	Interferes with assay (P, CR) without toxic effects
Diuretic: Lasix	*Panax ginseng*	Decreased therapeutic effect	Diuretic resistance with ginseng; unknown mechanism (CR)
Diuretic: Potassium sparing	Licorice	Decreased therapeutic effect	Interferes with potassium-sparing effects by wasting K^+
Estrogen replacement therapy	a. Herbs high in phytoestrogens (e.g., soy, fenugreek, licorice, black cohosh) b. *Panax ginseng*	a. Increased therapeutic effect to excess b. Increased side effect (estrogen excess)	a. Never reported (TH) b. Reported in few cases to produce postmenopausal bleeding or mastalgia (CR)
General medication	High-fiber herbs (e.g., flax, psyllium, acacia, slippery elm, marshmallow)	Decreased absorption	(P)
General medication	"Hot" remedies (e.g., ginger, garlic, black pepper, red pepper)	Increased absorption	Taken internally, "hot" remedies lead to vasodilatation of gut wall and increased absorption (TU)
GI motility drugs	Anticholinergic herbs (not generally used clinically, e.g., belladonna)	Decreased activity	Opposition of therapeutic activity
Hepatotoxic drugs	Hepatotoxic herbs (e.g., borage, coltsfoot, comfrey, rue, tansy)	Increased side effect (hepatotoxicity)	Additive toxicity from similar side effects (CR)
Hypoglycemic agents: Oral and insulin	Hypoglycemic (e.g., *Panax ginseng*, garlic, fenugreek, bitter melon, aloe, gymnema)	Enhanced therapeutic effect	a. Direct hypoglycemic activity (CR, AS, P) b. Decreased glucose absorption
Hypoglycemic agents: Oral and insulin	Hyperglycemic (e.g., cocoa, rosemary, stinging nettle)	Decreased therapeutic effect	Direct opposition of therapeutic action (CS)
Immune suppressants	Echinacea, astragalus	Opposition of therapeutic action	General immune stimulation by these herbs may interfere with ability of immunosuppressive drugs to prevent tissue rejection; never reported (TH)

Drug Category	Herbs	Herb Effect	Mechanism (Evidence Type)
Iron	Tannin-rich herbs (e.g., caffeine-containing herbs, cat's claw, tea, uva ursi)	Decreased therapeutic effect	Tannin binds with iron, decreasing absorption (TH, P)
Lithium	Diuretic herbs (e.g., celery seed, corn silk, horsetail, juniper)	Increased side effects	Decreased sodium leads to increased lithium toxicity
Lower seizure threshold (drugs that)	GLA-rich herbs (e.g., evening primrose, borage, black currant)	Increased side effect to additive side effect	Decreased seizure threshold (CR)
Methotrexate and similar cytotoxic drugs	Salicylate herbs (e.g., cramp bark, willow, wintergreen)	Increased plasma levels (toxicity)	Decreased excretion (TH)
Minerals	Fiber-containing herbs (e.g., flax, psyllium, acacia, slippery elm, marshmallow)	Decreased bioavailability	Psyllium has been reported to decrease the absorption of Ca, Mg, Cu, Zn (CR)
Monoamine oxidase inhibitors (MAOIs)	*Panax ginseng*, bioactive amines, licorice	Increased side effects	Additive side effects may lead to toxicity; glycyrrhizin is reported to be a very potent MAOI (TH, CR)
Monoamine oxidase inhibitors (MAOIs)	Ginkgo	Increased therapeutic effect; increased side effects	Inhibition of monoamine oxidase (P)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Gastric irritant herbs (e.g., caffeine, rue, uva ursi)	Increased side effects	Similar side effects may increase risk of gastric erosion and bleeding (TH)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Nettles	Increased therapeutic effect	Potentiation of the anti-inflammatory activity of NSAIDs (CT)
Opioids	*Panax ginseng*	Decreased therapeutic effects	Animal model demonstrated the blunting of the analgesic effects of morphine via a non-opioid receptor-mediated mechanism (AS)
Photosensitizing drugs	Photosensitizing herbs (e.g., St. John's wort, angelica, rue, fennel)	Increased side effects	Furanocoumarins found often in umbelliferae resemble psoralens (P, AS, CR)
Salicylates	Herbs that alkalinize urine (e.g., uva ursi)	Decreased plasma levels	Increased urinary excretion (P)
Sedative hypnotics	Opioid herbs (e.g., opium poppy, California poppy)	Increased side effects (CNS depression)	Additive side effects

Drug Category	Herbs	Herb Effect	Mechanism (Evidence Type)
Sedative hypnotics including alcohol	Sedative herbs (e.g., hops, kava, valerian)	Increased therapeutic action; increased side effects (CNS depression)	Additive effects lead to CNS depression *except* valerian does not potentiate the effects of alcohol (AS, P)
SSRIs	St. John's wort	Increased therapeutic activity; increased side effects	May contribute to serotonin syndrome—similar action (TH)
Statin drugs	Red yeast (Cholestin®)	Increased therapeutic effect	Similar active compounds; not known if taking both products simultaneously increases side effects of statin drugs (TH)
Thyroid hormone	a. Horseradish	a. Decreased therapeutic effect	a. Depressed thyroid function
	b. Kelp	b. Increased therapeutic effect	b. Iodine in kelp may result in hyperthyroidism (TH)