

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

by Milo Gibaldi, Ph.D., School of Pharmacy

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Written by Milo Gibaldi, Ph.D.

Edited by Nelda A. Murri, Pharm. D.

Prepared by Sandra Walston, M.C.

(206) 598-6612/nelda@u.washington.edu

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DRUG EVALUATION

Warfarin, Aspirin, or Both After Myocardial Infarction

Forty years ago, warfarin was administered routinely after a heart attack to decrease the risk of subsequent cardiovascular events. This practice fell into decline and aspirin replaced warfarin for this purpose. A recent report suggests that it is time to return to this pre-aspirin era [*N Engl J Med* 2002;347:969-74].

The importance of thrombosis in the pathogenesis of acute myocardial infarction is well recognized. Both oral anticoagulants and platelet-inhibiting drugs offer demonstrated benefits in this setting. In theory, the combined use of warfarin and aspirin might have an additive effect by suppressing both the coagulation cascade and platelet function. This, however, has been difficult to confirm in clinical trials.

In the new study, investigators randomly assigned 3630 patients who had survived an acute MI to receive warfarin (in a dose intended to achieve an international normalized ratio [INR] of 2.8 to 4.2), aspirin (160 mg daily), or aspirin (75 mg daily) combined with warfarin (in a dose intended to achieve an INR of 2.0 to 2.5). The mean duration of observation was four years.

Of the patients receiving aspirin alone, 20.0% experienced the composite endpoint—death, nonfatal reinfarction, or thromboembolic stroke—compared with 16.7% of patients receiving warfarin alone and 15.0% of patients receiving warfarin combined with aspirin. Warfarin, either alone or with aspirin, was more effective than aspirin alone, but the difference between the two groups receiving warfarin was not statistically significant. The beneficial effect of warfarin was restricted to nonfatal reinfarction and thromboembolic stroke; there was no statistically significant difference in overall mortality among the groups. Episodes of major, nonfatal bleeding were observed in 0.62% of patients per treatment-year in both groups receiving warfarin, and in 0.17% of patients receiving aspirin.

The absolute difference in benefit for warfarin versus aspirin was 3.3%, suggesting that 30 patients must be treated with warfarin rather than aspirin to avoid one nonfatal reinfarction or thromboembolic stroke. The absolute difference in major bleeding risk for warfarin versus aspirin was 0.45%, suggesting that, for every 222 patients treated with warfarin rather than aspirin, there will be one additional bleeding episode. The use of warfarin rather than aspirin also incurs substantial costs for regular monitoring of coagulation status.

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DRUG EVALUATION (continued)

Warfarin, Aspirin, or Both After Myocardial Infarction (continued)

The principal investigators told *Reuters Health* [26 September 2002], “Although there were more bleeding episodes during warfarin treatment, the benefit is still in favor of warfarin treatment and the combined therapy.” He added, “I think all patients, younger than 75 years of age, surviving a myocardial infarction should be considered for secondary preven-

tion with warfarin plus aspirin or warfarin alone, if there are no contraindications and if patient compliance is likely.” A companion editorial diplomatically rejects this idea, suggesting “it is likely that antiplatelet therapy will remain the standard of care in many countries for secondary prevention after myocardial infarction” [*Ibid*, 1019-21].

Early Aspirin Safe and Effective After CABG Surgery

There is no therapy known to reduce complications and death after coronary artery bypass graft (CABG) surgery. Although platelet activation constitutes an important mechanism for injury in patients with atherosclerosis, many physicians believe that giving aspirin to patients too soon after surgery will cause severe bleeding. This is a huge issue. In 1999, 355,000 Americans, most of whom were at high risk for complications, had bypass surgery. Now, a bold research group has tackled this question and their efforts were richly rewarded [*N Engl J Med* 2002;347:1309-17].

The investigators prospectively studied 5065 patients undergoing CABG surgery, of whom 5022 survived the first 48 hours after the procedure. During hospitalization, 164 patients died (3.2%); 1812 others (16%) had nonfatal cardiac, cerebral, renal, or gastrointestinal ischemic complications. Among patients who received aspirin (up to 650 mg) within 48 hours after revascularization, subsequent mortality was 1.3%, as compared with 4.0% among those who did not receive aspirin during this period. Aspirin therapy was

associated with a reduction in incidence of myocardial infarction (2.8% vs. 5.4%), stroke (1.3% vs. 2.6%), renal failure (0.9% vs. 3.4%), and bowel infarction (0.3% vs. 0.8%). Aspirin therapy also proved safe, incurring no increased risk of hemorrhage, gastritis, infection, or impaired wound healing.

One leading cardiologist said that the study is likely to change medical practice. Another opined that early aspirin use after bypass surgery should become the standard of practice. However, a note of caution is warranted. The study was not a randomized controlled trial. Patients were not selected at random to receive aspirin or not. Rather, their physicians decided on treatment. Physicians participating in the study may have been reluctant to prescribe aspirin for the sickest patients, whose adverse outcomes may have had more to do with their underlying disease rather than with aspirin. Alternatively, the physicians who prescribed aspirin may be more progressive than those who did not, and their patients may have received better overall care.

Nucleoside Therapy Prior to HAART Increases Risk of Virus Rebound

Even a short period of monotherapy or dual therapy with nucleoside reverse transcriptase inhibitors before highly active antiretroviral therapy (HAART) confers an increased risk of virus rebound. This is the principal finding of a survey of 1433 HIV-infected patients who achieved viral suppression—viral load < 400 copies/ml—within 24 weeks after first starting HAART. Of these patients, 409 had received previously one or two nucleosides and 1024 were naïve to antiretroviral agents.

During the course of observation, 307 patients experienced virus rebound—two consecutive virus load

measurements of > 400 HIV RNA copies/ml. There was a significantly higher rate of virus rebound among the patients who previously received nucleoside therapy (relative hazard, 2.86). The results confirm previous research. The new study also found that the risk of viral rebound was elevated even for patients who used nucleoside therapy for less than two months before beginning HAART (RH, 1.95). Among both nucleoside-experienced and drug-naïve patients, the risk of viral rebound decreased as the duration of viral suppression increased. But the greater risk for nucleoside-experienced patients compared

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Nucleoside Therapy Prior to HAART Increases Rebound Risk (continued)

with drug-naïve patients persisted into the third year of viral suppression [*J Infect Dis* 2002;186:1086-91].

Thus, inadequate initial treatment of HIV infection may compromise the ability to contain the virus for

months or even years to come. The findings also have consequences for the use of short-term monotherapy regimens in pregnant women to avoid transmission to their offspring.

DRUG SAFETY

COX-2 Selective NSAIDs and Risk of Coronary Heart Disease

Studies have raised doubts about the cardiovascular safety of the COX-2 selective NSAID rofecoxib (*Vioxx*). The results of a large gastrointestinal safety trial, indicated that individuals who took rofecoxib 50 mg/day were five times more likely to have a myocardial infarction than were those who took naproxen 1000 mg/day. Unlike naproxen, rofecoxib has no effect on platelets. Therefore, whether rofecoxib increases the risk of coronary heart disease (CHD) or naproxen has a cardioprotective effect was unclear.

To investigate further, researchers compared risk of acute MI and fatal CHD in users of rofecoxib with risk in nonusers and users of other frequently prescribed NSAIDs who were enrolled in the Tennessee Medicaid program. The study included an *a priori* analysis of rofecoxib at doses greater than 25 mg/day. The FDA does not recommend such doses for long-term (> 5 days) use and they may be uniquely associated with harm. The

cohort included 251,046 NSAID users and 202,916 non-users.

Those who used rofecoxib were 1.70 times more likely to develop serious CHD than nonusers and 1.78 times more likely than celecoxib (*Celebrex*) users. New users of rofecoxib had nearly a doubled risk. There was no evidence of increased risk of serious CHD for rofecoxib 25 mg or less, celecoxib, naproxen, and ibuprofen. Risk of serious CHD did not increase among high dose users of celecoxib (> 300 mg), naproxen (>1000 mg), or ibuprofen (>1800 mg).

The authors of the report say, "Our data, in conjunction with premarketing data—that suggest that high-dose rofecoxib increases hypertension, lower extremity edema, and creatinine concentrations—raise serious doubts about the cardiovascular safety of the drug at doses of greater than 25 mg" [*Lancet* 2002;360:1071-73]. They recommend that long-term use of high-dose rofecoxib be avoided.

Considering the Risks and Benefits of *Accutane*

A recent issue of *The Medical Letter* [2002; 44:82] tackled the question, "Is *Accutane* really dangerous?" Prompting the inquiry was the nearing availability of generic versions of isotretinoin, the active ingredient of *Accutane*, and widely reported concerns about its adverse effects, especially psychiatric symptoms in adolescents. The reviewers concluded that *Accutane* is a remarkably effective drug for treatment of severe acne that has many adverse effects and is unequivocally teratogenic.

Isotretinoin, an oral vitamin A derivative that suppresses the activity of sebaceous glands, is the most effective treatment ever offered for acne. It

can completely clear severe lesions, leading to prolonged remissions that persist for years after treatment is discontinued. Isotretinoin is burdened with adverse effects, including dry, cracked skin, hair loss, elevated triglyceride levels, and hepatitis, among others, all characteristic of vitamin A toxicity. The most serious problem has been isotretinoin's teratogenicity, which has led to restrictions on its use by young women.

The association of isotretinoin use with psychiatric problems has waxed and waned over many years, but cause and effect has been difficult to establish. The only systematic study of the association, which

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DRUG SAFETY (continued)

Considering the Risks and Benefits of *Accutane* (continued)

compared more than 7000 isotretinoin users with more than 13,000 patients taking oral antibiotics for acne, found no difference between the two groups in psychiatric diagnoses or suicide risk.

The Medical Letter report on isotretinoin concluded, “There is no firm evidence that it causes

serious psychiatric disorders or suicide, but anecdotal evidence and extrapolation from hypervitaminosis A suggest it might. Until more data become available, the benefit from carefully monitored treatment of a disfiguring condition appears to outweigh the risk.”

NEW DRUGS AND INDICATIONS

Buprenorphine as Drug-Abuse Therapy

The FDA has approved two formulations of a new drug-abuse therapy, which, under a recent law passed by Congress, will become the first narcotic-substitute preparation in the U.S. that can be prescribed in a physician’s office [*Reuters Health*, 10 October 2002]. *Subutex* (buprenorphine) and *Suboxone* (buprenorphine and naloxone) are indicated for the prevention of withdrawal symptoms from heroin or other opioids. Both products consist of tablets meant to dissolve under the tongue. *Subutex* is intended for use at the beginning of treatment. *Suboxone*, which contains the narcotic antagonist naloxone to safeguard against intravenous drug abuse, is intended for maintenance treatment.

Buprenorphine, a partial agonist, is thought to have less risk of causing dependence than morphine, oxycodone, or methadone. Nevertheless, the Drug Enforcement Administration (DEA) would have placed the new products in Schedule II under the Controlled Substances Act. But earlier this year, congress approved legislation intended to facilitate the dispensing of buprenorphine by physicians and make it easier for

addicts to obtain therapy in areas that do support a methadone clinic. Accordingly, the FDA and the Department of Health and Human Services have recommended that the DEA place buprenorphine in Schedule III, a less restrictive class.

The approval of buprenorphine was based on clinical studies enrolling more than 2000 patients. They showed that both products were safe and effective. But the FDA also acknowledged reports from France, where buprenorphine has been available for several years, linking the drug to deaths from respiratory complications, especially when used in combination with alcohol or antidepressants. In conjunction with the FDA, the maker of *Subutex* and *Suboxone* has developed a risk management program designed to deter abuse and diversion. The program also includes provisions for surveillance. The FDA has the authority to limit the number of patients treated by individual physicians and to require physicians to obtain special registration from the DEA.

FDA OK’s Adefovir for Chronic Hepatitis B Infection

New, oral antiviral therapy, adefovir dipivoxil (*Hepsera*), is now available for the treatment of patients infected with hepatitis B virus (HBV). It is the third drug treatment—joining interferon and lamivudine—and the first nucleotide to be made available to treat this serious infection that sometimes leads to cirrhosis and liver cancer. Adefovir was originally tested as a possible treatment for HIV infection, but the dose required for efficacy precipitated nephrotoxicity. The dose needed to treat chronic hepatitis B infection is much

lower and has a better safety profile. In clinical studies, adefovir was associated with significant improvements in liver histology and fibrosis, reductions in serum HBV DNA levels, increases in rates of seroconversion, and normalizations of alanine aminotransferase as compared with placebo in treatment-naïve patients and in patients previously treated with interferon. The drug was also studied and proven effective in patients who were treated with and developed resistance to lamivudine.

Topical Aerosol Spray Lights Up Nits

Parents of children with head lice may wish to know of a new product that may make diagnosis and eradication easier. *Neon Nits* dyes head lice nits bright pink, making them easier to see and remove with a nit comb. The dye sticks to the polymer structure on the surface of the lice egg, but not so strongly to scalp and hair. It does not eliminate the nits by itself. The product is shampooed out of the hair after the nits are removed. The addition of bicarbonate to the shampoo

facilitates removal of the pink color. *Neon Nits* has a foul odor and should be applied lightly in a well-ventilated area. The National Pediculosis Association does not recommend the use of *Neon Nits*, expressing concern about the lack of studies that demonstrate its safety. In its tests, the association found the spray difficult to use and remove from the hair [*Prescriber's Letter* 2002;9:180910].

CLINICAL PRACTICE

UK Issues Guidelines for Type 2 Diabetes

Britain's National Institute for Clinical Excellence has issued clinical guidelines designed to reduce life-threatening complications of type 2 diabetes. The institute noted that the incidence of type 2 diabetes is on the increase in England and Wales and that poor glucose control raises the risk of ischemic heart disease and microvascular disease, such as diabetic retinopathy and nephropathy.

The guidelines recommend that people with type 2 diabetes should have their hemoglobin HbA1C measured every two to six months, with a target between 6.5% and 7.5%. Weight loss and increased physical activity should be encouraged, especially in those who are overweight or obese.

The guidelines also recommend the use of glucose-lowering drugs, such as metformin, insulin secreta-

gogues, and the glitazones. "For patients who are overweight (body mass index over 25) and whose blood glucose is inadequately controlled by lifestyle interventions, metformin should normally be used as first-line therapy" [*Reuters Health* 18 September 2002]. Insulin secretagogues—sulfonylureas, nateglinide, and repaglinide—should be used in combination with metformin if blood glucose levels begin to increase over time. These drugs could also be used for first-line therapy if metformin is not tolerated or if patients are not overweight. A glitazone should be considered, in combination with another hypoglycemic agent, for patients who are unable to take metformin or insulin secretagogues or if their HbA1C levels remain unsatisfactory despite an adequate trial of metformin with insulin secretagogues.

Task Force Report Helps Identify Those Best Served by Tamoxifen Prophylaxis

A report from the U.S. Preventive Services Task Force concerning chemoprevention of breast cancer helps identify women who might benefit from using tamoxifen [*Ann Intern Med* 2002;137:56-67]. The current estimate is that tamoxifen prevents 20 cases of invasive breast cancer for every 1000 high-risk women who take the drug for five years. But tamoxifen also causes serious adverse effects—blood clots, stroke, endometrial cancer, and cataracts—and prophylaxis should be strictly limited to certain high-risk women. Women are considered at high risk for breast cancer if they are over 40 and have a family history of breast cancer in a mother, sister, or daughter or have a history of atypical cells on breast biopsy. A risk assessment instrument based on age, family history, and other risk factors, developed by the National Cancer Institute, is available on-line at <http://www.cancer.gov/star>.

Tamoxifen is a good choice for high-risk women in their 40s if they have no risk factors for thrombosis. Tamoxifen is appropriate for high-risk women in their 50s if they have no risk factors for thrombosis and do not have a uterus. The risk of endometrial cancer from tamoxifen is higher in women over 50 than in younger women. Tamoxifen is not recommended in women over 60. Although these women have the highest risk of breast cancer, they also have the highest risk of complications from tamoxifen. Raloxifene (*Evista*) might be more appropriate for older women, in that it does not increase the risk of endometrial cancer, but it is not yet approved for preventing breast cancer [*Prescriber's Letter* 2002;9:180914].

Recently reported results from a randomized trial generally support the Task Force's recommendations. In
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Report Helps Identify Those Best Served by Tamoxifen Prophylaxis (continued)

the trial, women, 35 to 70 years of age, who were at increased risk for breast cancer, were randomly assigned to tamoxifen 20 mg/day or placebo for five years. Intention-to-treat analysis demonstrated that during a median follow-up of 50 months, 69 of 3566 women in the tamoxifen group developed breast cancer compared with 101 of 3566 women in the placebo group, an absolute risk reduction of 0.90% and a relative risk reduction of 32%. The data from this study suggest that tamoxifen prevents only 9 cases of breast cancer for every 1000 high-risk women who take the drug. The reduction in risk was not affected by age or degree of risk.

The risk of endometrial cancer increased 2.2 times among women receiving tamoxifen compared with placebo, and the risk of thrombotic events increased 2.5 times. There were significantly more deaths from all causes among women in the tamoxifen group compared with women in the placebo group. The authors concluded their report by noting, "At this stage, tamoxifen cannot be routinely recommended for prevention of breast cancer in high-risk women, and further follow-up of current trials is needed to identify which women are most likely to benefit from therapy" [*Lancet* 2002;360:817-24].

ALTERNATIVE MEDICINE

■ **Herbal Remedy for Prostate Health Heavily Contaminated with Synthetic Drugs.** Although legally sold in the U.S. since 1996 as a dietary supplement for "prostate health," PC-SPES is in fact a widely used alternative medicine treatment for prostate cancer. The PC in the name stands for prostate cancer and *spes* is Latin for hope. Prompted by allegations of contamination of the natural product, the California Department of Health Services decided to test lots of PC-SPES and found contamination with both the synthetic estrogen diethylstilbestrol (DES) and warfarin. This finding has now been independently verified [*J Natl Cancer Inst* 2002;94:1275-81]. The new report suggests that PC-SPES was also contaminated with indomethacin.

Discovering the adulteration of PC-SPES with synthetic drugs initiated a cascade of consequences. In February 2002, California's health department issued a warning on the contamination. At the same time, the California-based maker of PC-SPES, Botanic Labs, voluntarily recalled the product nationwide. The FDA published a medical product safety alert. Canada and Ireland also announced recalls of the product. A large clinical trial comparing PC-SPES and DES was stopped. In June 2002, the California Department of Health announced the contamination of several other herbal products sold by the same company. Botanic Labs went out of business on 1 June 2002 and PC-SPES is no longer available. Consequently, the National Center for Complementary and Alternative Medicine of the National Institutes of Health placed all of its funded grants using PC-SPES on hold pending further review.

The problem, however, may not have been eliminated. Products with similar names (i.e., PC-Calm, PC-Plus) and herbal composition are starting to fill the void. Whether these products are contaminated and pose a threat remains to be determined [*Ibid*, 1261-63].

■ **St. John's Wort Decreases Plasma Levels of Irinotecan Active Metabolite.** Added to the list of adverse drug interactions with St. John's wort is the antineoplastic agent irinotecan (*Camptosar*). Researchers warn that the popular herbal remedy for depression reduces plasma levels of the active metabolite of irinotecan [Sparreboom A, *J Natl Cancer Inst* 2002;94:1247-49].

St. John's wort induces expression of CYP3A4, an isoform of the cytochrome P450 drug metabolizing enzyme system. Irinotecan is a substrate for CYP3A4. To determine the significance of this potential interaction, the investigators conducted a randomized crossover study of cancer patients receiving irinotecan every three weeks. Starting two weeks before the first or second infusion, the patients took St. John's wort every day until four days after irinotecan dosing. The results showed that the average plasma levels for the active metabolite was 42% lower when irinotecan was given with St. John's wort than when it was given alone. The effect of the herb on plasma levels was detectable even three weeks after the last dose. The investigators predict that the same problem will be seen with the taxanes and other anticancer drugs, pointing out that more than 50% of drugs used to treat cancer are metabolized by CYP3A4 [*Reuters Health*, 22 August 2002].