

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

High-Normal Blood Pressure Poses Problems

Using the Framingham Heart Study database on 6859 participants who were initially free of hypertension and cardiovascular disease, investigators have shown that blood pressure now classified as high-normal is associated with an increased risk of cardiovascular disease [*N Engl J Med* 2001;345:1291-97]. Previous studies demonstrated that blood pressure has a strong, continuous, graded, and etiologically significant positive association with cardiovascular-disease outcomes. Nevertheless, classification according to blood pressure provides a framework for differentiating risk. Nonhypertensive patients with a systolic pressure of 130-139 mm Hg or a diastolic pressure of 85-89 mm Hg are categorized as having high-normal blood pressure. There is only limited information regarding the absolute and relative risks of cardiovascular disease in these patients.

The investigators determined that the 10-year cumulative incidence of cardiovascular disease in subjects 35 to 64 years of age who had high-normal blood pressure was 4% for women and 8% for men; in older subjects, those 65 to 90 years old, the incidence was 18% for women and 25% for men. As compared with optimal blood pressure, high-normal blood pressure was associated with an adjusted hazard ratio of 2.5 in women and 1.6 in men. The authors of the report emphasized the need to determine whether lowering high-normal blood pressure can reduce the risk of cardiovascular disease. A related editorial considers the findings an important advance in our understanding of the magnitude of the problem presented by hypertension [*Ibid*, 1337-40].

Olanzapine Reduces Tardive Dyskinesia Symptoms

Lilly Research Laboratories reported that the antipsychotic medication olanzapine (*Zyprexa*) produced a sustained improvement in tardive dyskinesia symptoms in patients with schizophrenia. In the study, 95 patients—60% with schizophrenia, 27.4% with schizoaffective disorder, and 12.6% with schizophreniform disorder—were treated with olanzapine 5 to 20 mg daily for eight months. Tardive dyskinesia had been evident in the patients for a mean of 4.8 years, and the mean cumulative exposure to antipsychotic agents was 3.5 years during the five years prior to the study. The investigators observed a significant improvement in tardive dyskinesia symptoms as early as one week into treatment. By the end of 32 weeks of treatment, about 70% of patients were no longer classified as having tardive dyskinesia. The treatment protocol included two 2-week periods in which the dose of olanzapine was reduced by at least 75% to allow for the possibility of tardive dyskinesia rebound, but rebound did not occur [*Reuters Health*, 15 October 2001].

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CLINICAL PRACTICE (continued)

Experts Recommend New Classification of Heart Failure

The American College of Cardiology (ACC) and the American Heart Association (AHA) have released a new classification system for heart failure designed to complement the New York Heart Association (NYHA) functional class system. Under the new system, heart failure is defined in stages A to D. Patients in stage A are asymptomatic and have no heart damage, but have risk factors for heart failure. Those classified as being in stage B are asymptomatic but have signs of structural heart damage. Patients in stage C are those with heart damage and who have symptoms, while those in stage D have endstage disease. Patients in stages A and B would all be categorized as NYHA

class I because they are asymptomatic. The ACC/AHA system borrows concepts from cancer staging. For example, heart failure patients who cross the line from asymptomatic disease and develop symptoms, irrevocably cross into stage C. A patient's symptoms might improve with treatment and go back to NYHA class I, but the patient will still be in stage C. The new guidelines are available online at www.acc.org or www.americanheart.org. They can also be found in the December 2001 issue of the *Journal of the American College of Cardiology* and the 11 December 2001 issue of *Circulation*.

DRUG SAFETY

Hormone Replacement Therapy and Dry Eye Syndrome

Dry eye syndrome, one of the leading causes of patient visits to both ophthalmologists and optometrists, damages the ocular surface and can cause symptoms of dryness and irritation, which may result in psychological comorbidity and reduced work capacity. The syndrome is associated with an enhanced risk of corneal infection, and, when severe, can cause permanent visual impairment. Hormone replacement therapy is used by nearly 40% of postmenopausal women in the U.S., but there are virtually no data on the relationship between HRT and dry eye syndrome. Therefore, investigators examined this relationship in the Women's Health Study, a large cohort study in which 25,665 postmenopausal women pro-

vided information about HRT use and an array of health outcomes.

For the combined end point of either clinically diagnosed dry eye syndrome or severe symptoms, the multivariable-adjusted odds ratios at 48 months were statistically significant—1.69 for estrogen use alone and 1.29 for estrogen plus progestin use, compared with no HRT use. Each three-year increase in the duration of HRT use was associated with a significant 15% elevation of the combined end point. These data suggest that women who use HRT, particularly estrogen alone, are at increased risk of dry eye syndrome [*JAMA* 2001;286:2114-19].

Helicobacter Pylori and NSAIDs

Whether *Helicobacter pylori* increase the risk of ulcers in patients taking nonsteroidal anti-inflammatory agents (NSAIDs) is controversial. Nevertheless, some experts think that eradication of *H. pylori* infection would reduce the risk of ulcers for patients starting long-term NSAID treatment. Two papers in a recent issue of *The Lancet* go some way in supporting this hypothesis.

Through a search of the literature, investigators at McMaster University identified 25 observational studies on the prevalence of peptic ulcer disease in users of NSAIDs in the presence or absence of *H. pylori* infection. They found that peptic ulcer disease in NSAID-takers was significantly more common among people who were positive (42%) than among those negative (26%) for *H. pylori*. In case-control

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***Helicobacter Pylori* and NSAIDs** (continued)

studies, NSAID-takers with *H. pylori* infection were 61 times more likely to have a peptic ulcer than were noninfected nontakers. Either factor alone increased the risk 20-fold. They also found that *H. pylori* infection and NSAID use increased the risk of ulcer bleeding by 1.79-fold and 4.85-fold, respectively, but together they increased the risk by 6.13-fold. The findings suggest synergy between the two kinds of damage to the gastroduodenal mucosa [*Lancet* 2002;359:14-22].

Investigators from Hong Kong reported on an intervention study in which patients were enrolled if they were NSAID naïve, had a positive urea breath test (indicative of an *H. pylori* infection), had dyspepsia or an ulcer history, and required long-term NSAID treatment. The patients were randomly assigned to triple eradication therapy—omeprazole plus

amoxicillin and clarithromycin—or omeprazole alone for one week. All patients were given diclofenac slow release for six months from randomization. The six-month probability of ulcers found endoscopically was 12% in the triple eradication group and 34% in the omeprazole-alone group. The frequency of complicated (symptomatic and bleeding) ulcers was 4% in the triple eradication group and 27% in the omeprazole-alone group [*Ibid*, 9-13].

The work of the McMaster investigators confirms that both *H. pylori* infection and NSAID use increase the risk of peptic ulcer and ulcer bleeding; this demonstrates a substantial synergy between infection and NSAID use. The researchers also stressed that peptic ulcer disease is rare in *H. pylori*-negative, non-NSAID takers [*Ibid*, 14-22].

Liver Warning for Serzone

The FDA has notified Bristol-Myers Squibb that it must include a black-box warning on its label for the antidepressant *Serzone* (nefazodone) advising that rare but potentially life-threatening liver toxicity can occur with use of the drug. The agency will also require Bristol-Myers to warn physicians by letter that a small number of patients could suffer liver failure leading to death or necessitating a liver transplant. The FDA estimates a reported rate of one case of liver failure for every 250,000 to 300,000 patients

using the drug for one year, a rate of about 3-4 times the estimated background rate of liver failure. *Serzone* is regarded as an important alternative to specific serotonin reuptake inhibitors for patients who suffer sexual dysfunction. Canadian regulators issued a similar warning six months before the FDA acted. Psychiatrists said the warning labels for *Serzone* will hurt the drug's sales, now at \$400 million a year [*The Wall Street Journal Interactive Edition*, 7 December 2001].

Boxed Warning for Preoperative Droperidol

The FDA has strengthened the warning in the labeling for injectable droperidol—used in the U.S. as preoperative medication to promote sedation and reduce nausea and vomiting—after the drug was linked to fatal cardiac arrhythmias when administered at or even below recommended doses. The FDA said there have been reports of torsade de pointes associated with QT prolongation. Injectable droperidol will now carry a “black box” warning, the most serious caution assigned to drugs approved

for sale in the U.S. The FDA's action has resulted in the removal of three indications from labeling: tranquilization after surgical and diagnostic procedures; premedication induction, and as an adjunct in the maintenance of general and regional anesthesia; and use in neuroleptanalgesia to aid in producing tranquility and decrease anxiety and pain” [*The Pink Sheet*, 10 December 2001]. New labeling also reduces the recommended dose for droperidol.

NEW DRUGS AND INDICATIONS

FDA Approval to Oral Pulmonary Hypertension Drug

Actelion Ltd. has received approval from the FDA to market *Tracleer* (bosentan), its orally effective endothelin receptor antagonist for the treatment of pulmonary hypertension. The only other approved therapy for this rare but potentially fatal condition is *FloLAN* (epoprostenol), which requires intravenous infusion. On approving the novel drug, the FDA also stipulated that use of *Tracleer* would be limited to a direct distribution program because of the drug's possible side effects, including potential liver toxicity and teratogenicity, and that the drug would not be available in community pharmacies. Ongoing phase III trials are evaluating bosentan for the treatment of heart failure [*Reuters Health*, 26 November 2001].

Novartis's *Elidel* Approved for Eczema

Elidel (pimecrolimus), a topical immunomodulator, has been approved for use in eczema, but only for patients two years old or older. The restriction is a disappointment for Novartis, which filed phase III data from babies as young as three months. The approved indication is for short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in patients who do not respond well to or are intolerant of conventional treatments. *Elidel* will compete directly with *Protopic* (topical tacrolimus), which is already available in the U.S. [*Scip*, 19 December 2001].

Novartis plans to file a supplemental New Drug Application for *Elidel* in younger patients once it resolves questions raised by the FDA about two phase III studies of 436 infants aged 3 to 23 months. While no infant discontinued treatment in the six-week trial, there was an increased incidence of some

adverse events compared with the vehicle. Novartis maintains that the adverse events—pyrexia, upper respiratory infection, nasopharyngitis, gastroenteritis, otitis media, and diarrhea—indicate typical childhood illnesses, and the increase in overall adverse events for *Elidel* compared with placebo is not statistically significant. Novartis argues that *Elidel* is well suited for infants because, unlike topical steroids, pimecrolimus has no potential for skin atrophy and discoloration and no potential for growth retardation [*The Pink Sheet*, 17 December 2001].

FDA Approves *Kineret* for Rheumatoid Arthritis

Amgen has received approval from the FDA to market *Kineret* (anakinra) to reduce the signs and symptoms of moderate-to-severe active rheumatoid arthritis in adult patients who have failed conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. *Kineret*, given by subcutaneous injection, is the first selective blocker of interleukin-1 (IL-1) to be approved in the U.S. The new product will be priced at \$924 for a four-week supply, somewhat less than the tumor necrosis factor (TNF)-blockers *Enbrel* (etanercept) and *Remicade* (infliximab), both of which are also indicated to slow disease progression. As second-line therapy, *Kineret* may be prescribed alone or in combination with DMARDs other than TNF-inhibitors. Approval was based on clinical trials showing that 38% of patients in the active treatment group achieved a 20% improvement in ACR criteria within six months compared with 22% of patients in the placebo group who achieved that level of benefit. The most common side effect was mild injection-site reaction. *Kineret* also carries a small risk of serious infection, which may be increased if *Kineret* were to be given with *Enbrel* or *Remicade* [*Reuters Health*, 15 November 2001].

DRUG EVALUATION

Largest Secondary Prevention Trial Demonstrates Remarkable Benefits for Statin

Findings from The Heart Protection Study, presented at the American Heart Association Scientific Sessions 2001, the largest secondary prevention trial ever conducted, show that simvastatin (*Zocor*) reduced the risk of an acute myocardial infarction or a stroke by

one-third in an extraordinarily diverse group of 20,536 high-risk patients with hypertension, coronary artery disease, other occlusive artery disease, and/or a history of acute MI, other heart disease,

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Secondary Prevention Trial Demonstrates Statin Benefits (continued)

stroke, or diabetes. Participants included large numbers of women, elderly people, people with diabetes, and people with average or below-average cholesterol levels [*Reuters Health*, 14 November 2001].

The patients were randomly assigned to one of four treatment arms: monotherapy with simvastatin 40 mg/day; simvastatin and antioxidant vitamins (vitamins C and E and beta-carotene); vitamins alone; or placebo. Patients also received, as appropriate, aspirin, anticoagulants, nitrates, beta-blockers, ACE inhibitors, calcium channel blockers, and nonstudy statins. They were followed for an average of five years. Simvastatin reduced all-cause mortality, cardiovascular mortality, major cardiac events, strokes, and revascularization procedures by one-third in all high-risk groups, including women, patients over age 70, and patients with dia-

betes. Risk reduction also occurred in patients with LDL cholesterol levels below 120 mg/dl, a group not usually targeted for statin therapy. On the other hand, there was no evidence of any benefit from antioxidant vitamins.

Simvastatin was well tolerated, with a very low incidence of elevated liver enzymes (0.8% in the simvastatin group compared with 0.6% in the placebo group) and elevated muscle enzymes (0.09% compared with 0.05% in the placebo group) [*Ibid*]. According to the lead investigator, about 25 million people worldwide now take statins. The new findings suggest that 200 million people would benefit from statin therapy. He also said that if 10 million high-risk patients started taking statins, 50,000 deaths would be prevented each year [*The New York Times on the Web*, 14 November 2001].

Rofecoxib Seems Superior for the Treatment of Osteoarthritis of the Knee

Although nonsteroidal anti-inflammatory drugs have long been used to treat the pain and stiffness associated with osteoarthritis, the American College of Rheumatology guidelines, updated in 2000, recommend acetaminophen as first-line therapy. To resolve this duality, investigators estimated the efficacy of rofecoxib (*Vioxx*) 12.5 or 25 mg/day, celecoxib (*Celebrex*) 200 mg/day, and acetaminophen 4000 mg/day in 382 adult patients with previously treated osteoarthritis of the knee [*JAMA* 2002;287:64-71].

Overall, 79% of the patients completed the six-week study. More patients treated with acetaminophen discontinued early because of lack of efficacy than did patients treated with the COX-2 selective inhibitors rofecoxib and celecoxib (31% vs. 18-19%). Efficacy assessed in the first six days of therapy, based on pain

on walking, night pain, pain at rest, and morning stiffness, was highest for rofecoxib 25 mg/day, followed by rofecoxib 12.5 mg/day, celecoxib, and acetaminophen. Over six weeks, rofecoxib 25 mg/day provided the greatest response for night pain, a composite pain scale, a stiffness subscale, and a physical function subscale. Good or excellent responses on a global scale were recorded in 60% of patients on rofecoxib 25 mg/day, 56% on rofecoxib 12.5 mg/day, 46% on celecoxib, and 39% on acetaminophen. All treatments were well tolerated. Merck & Co., the maker of *Vioxx*, supported the study. The findings notwithstanding, it seems sensible in light of cost considerations to start treating patients with osteoarthritis of the knee with a course of acetaminophen 4000 mg/day. If this is not successful, then other therapies including rofecoxib should be considered.

NSAIDs Appear to Lower Risk of Alzheimer's Disease

Inflammatory mechanisms have been proposed as important mediators in the pathogenetic cascade of Alzheimer's disease. Laboratory studies and case-control epidemiologic investigations from the early 1990s suggest that anti-inflammatory treatment, and in particular the use of nonsteroidal anti-inflammatory drugs (NSAIDs), was associated with delayed or reduced occurrence of Alzheimer's disease. More recent findings, however, have been mixed. Now researchers report the results of a prospective, population-based cohort study of 6989 people 55 years of age or older who were free of dementia at baseline. They examined

the association between the use of NSAIDs, as documented in pharmacy records, and development of dementia. During an average follow-up period of 6.8 years, dementia developed in 394 participants, of whom 293 had Alzheimer's disease.

The research team found that people who used NSAIDs for at least two years were 80% less likely to develop Alzheimer's disease than individuals who used these drugs for shorter periods or who did not use them at all. The risk of Alzheimer's decreased with the num-

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NSAIDs Appear to Lower Alzheimer's Risk (continued)

ber of years that patients continued to take the drugs. Risk reduction was unrelated to NSAID dose or the participant's age at baseline [*N Engl J Med* 2001; 345:1515-21]. In light of these findings, primary prevention trials should be undertaken to confirm them and determine whether the benefits of such therapy

outweigh the potential risks. One such trial, the Alzheimer's Disease Anti-inflammatory Prevention Trial, has been initiated to evaluate the ability of the NSAID naproxen as well as of the selective cyclooxygenase-2 inhibitor celecoxib (*Celebrex*) to prevent Alzheimer's disease [*Ibid*, 1567-68].

Intensive Insulin Therapy in Critically Ill Patients

Hyperglycemia associated with insulin resistance is common in critically ill patients, even those who are not diabetic. In such patients with protracted critical illness, high serum levels of insulin-like growth factor-binding protein 1, which reflect an impaired response of hepatocytes to insulin, increase the risk of death. Hypothesizing that hyperglycemia during critical illness may confer a predisposition to complications, such as polyneuropathy, multiple organ failure, and death, clinical researchers initiated a well-controlled trial to determine whether normalization of blood glucose levels with intensive insulin therapy reduces mortality and morbidity among critically ill patients [*N Engl J Med* 2001;345:1359-67].

On admission to a surgical intensive care unit, 1548 adult patients requiring mechanical ventilation were randomly assigned to receive intensive insulin therapy to maintain blood glucose between 80 and 110 mg/dl or conventional treatment (insulin infusion if blood glucose

level exceeded 215 mg/dl and maintenance of glucose between 180 and 200 mg/dl). Mortality was 8.0% in those patients who received conventional therapy and 4.6% in those who received intensive insulin therapy. The benefit of intensive therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days. The greatest reduction in mortality involved deaths due to multiple organ failure with a proven septic focus.

A second report in the same issue of the *Journal* also concerned the benefits of restoring aberrant respiratory, cardiovascular, and other functions to physiologic levels in critically ill patients [*Ibid*, 1368-77]. In this study, investigators evaluated the effects of early goal-directed therapy designed to balance tissue oxygen demand and oxygen delivery in patients with severe sepsis, septic shock, or the sepsis syndrome. In-hospital mortality was 30.5% in the group assigned to early goal-directed therapy and 46.5% in the group assigned to standard therapy.

DRUGS IN DEVELOPMENT

Pegvisomant, A Growth Hormone Receptor Antagonist for Acromegaly

Acromegaly is usually caused by an adenoma of the pituitary. Current treatments attempt to control the disease by reducing growth hormone secretion from the tumor by surgery, radiotherapy, or medication. Surgery cures only 60% of patients, and radiotherapy remains limited. Medical therapy with dopamine agonists or somatostatin analogs is also less effective than desired.

Pegvisomant (*Somavert*) is a new genetically engineered analog of human growth hormone that functions as a selective growth hormone receptor antagonist. Investigators assessed the treatment efficacy of pegvisomant in 152 patients with acromegaly who received the drug daily by subcutaneous injection for up to 18 months [*Lancet* 2001;358: 1754-59]. Of

those treated for at least 12 months, 97% achieved a normal serum insulin-like growth factor-1 (IGF-1) concentration. The response rate is high compared with the approximately 65% obtained with existing medical therapies. The improved response is attributed to pegvisomant's mechanism of action, by which the effect of excess growth hormone is blocked at a cellular level, rather than relying on inhibition of growth hormone secretion from the tumor.

The principal investigator told *Reuters Health* [27 November 2001], "Clinically this drug reverses all those symptoms that are reversible. Obviously, once the bones have grown, there's not much you can do about that. But the soft tissue swelling goes down and the sweating stops and the diabetes improves."