COX-2 Inhibitors: The Rise and Fall (continued from page two)

of people figure skating, doing yoga, and playing guitar comfortably on their couches. Both drugs caught on big time, selling better than drugs for erectile dysfunction (go figure!). The potential cardiac risk could be neglected by concomitant low-dose aspirin, couldn’t it? But wouldn’t this negate the GI protective benefit?

Events of the past few months in particular have not answered any of the questions, but things have become simpler. As the coubs were studied for their potential in preventing colon cancer and Alzheimer’s disease, a clear cardiovascular risk was demonstrated again with rofecoxib and for the first time with celecoxib (in higher doses). A newer agent (valdecoxib) increased postoperative pain relief after cardiac surgery. Rofecoxib was voluntarily removed, and valdecoxib followed more recently. We are left with celecoxib and many questions. Is the cardiovascular risk from COX-2 inhibitors related to the hypertension and fluid retention common to all NSAIDs, or is it the lack of platelet inhibition along with an effect on endothelial prostaglandins, or both? Is the cardiovascular risk temporary or more lasting, and does this apply to all patients or only a selected few?

In the end, we are still challenged to make NSAIDs less risky when we use them. Patients at low risk for GI complications should be treated with nonselective NSAIDs, and should have been all along. For patients with GI risk factors, concomitant proton-pump inhibitor (PPI) or misoprostil therapy reduce the ulcer risk in most studies, and celecoxib may not have much cardiovascular risk at lower doses. In addition, we really shouldn’t forget that there is always an alternative to an NSAID (e.g. low-dose steroid in RA, pure analgesics and local measures in osteoarthritis, tendinitis and bursitis).

Maybe we really don’t need a safer aspirin as much as we thought!

Contributed by Christopher Wise, MD
Professor of Medicine and Director, Medical Subspecialties Clinics, Department of Internal Medicine

Keeping Healthy

Recent reports addressing trends in the cardiovascular and overall death risks associated with obesity (JAMA. 2005; 293: 1861 and 1868) have prompted this brief invited commentary about how and what our departmental members should be doing to stay healthy. For the sake of simplicity, I assume your age is less than 50 and I will not discuss women’s health issues.

Following are selected principles that the U.S. Preventive Services Task Force (http://www.ahcpr.gov/clinic/uspstfix.htm) directs us as practitioners what we should all remember as individuals.

1. Pick your parents wisely! If you do not have a family history of some important illness, for 90% of the conditions addressed in the USPTF the conclusion was that screening testing had ‘insufficient’ evidence to recommend for or against.
2. Your personal practices are key “WELLNESS” behaviors.
3. Advice, counseling on injury prevention (seatbelts, helmets, etc.), or shared decision-making conversations – not tests – should be dominant in your visits with a physician.
4. While the frequency of checking can be debated, all of us should know our blood pressure recordings and last cholesterol levels.
5. Almost no one gains muscle mass after the age 28–30, so every pound gained increases your risk of multiple unpleasant conditions. While the JAMA article showed a temporal trend for less severe cardiovascular risks (blood pressure, cholesterol, glucose and smoking) associated with obesity, the popular press did not highlight that fact. I suspect this happens because a much greater number of people are now being treated for these conditions and the relative frequency of treatment tracks with weight.
6. For those of you who must do something, the only pre-emptive supplements I recommend are pre-natal vitamins with folic acid for women planning or capable of pregnancy, calcium carbonate 500–1000 mg per day, and a baby aspirin. Of these latter, I remember at least twice a week!

Contributed by Bruce E. Hillner, MD
Associate Chair for Information Technology, Department of Internal Medicine
COX-2 Inhibitors: The Rise and Fall

All we ever wanted was a safer aspirin!

The new non-steroidal anti-inflammatory drugs (NSAIDs) introduced during the 1970s and 1980s promised to reduce the frequency and severity of the well-known toxicities of aspirin-like drugs. However, by the early 1990s, the widespread use of NSAIDs was still placing large numbers of patients at risk for significant GI toxicities, including ulcers, perforations and bleeds. The discovery of cyclo-oxygenase isoenzymes, the “housekeeping” COX-1, responsible for gastric protection and platelet aggregation, and the “inducible” COX-2, suggested that we might be able to develop “selective” NSAIDs that could relieve pain and inflammation and not irritate the gastric mucosa.

The 1990s saw the development of agents highly specific for COX-2 (the coxibs). Early clinical trials showed that these agents provided the same (but not better) level of pain relief as traditional NSAIDs with fewer endoscopic gastric lesions initially. Eventually celecoxib (Celebrex) and rofecoxib (Vioxx) were approved for use after larger studies demonstrated fewer GI complications compared to nonselective NSAIDs. However, things weren’t nearly as simple as they might have seemed. Studies with celecoxib (where concomitant aspirin was allowed) didn’t show the statistically significant level of ulcer reduction that rofecoxib did, and some studies with rofecoxib (where no aspirin was allowed) suggested an increased risk of cardiac events when compared to a nonselective NSAID (naproxen).

In spite of the questions, most of us felt that patients at risk for GI complications would be safer on coxibs, and our patients were highly impressed by advertisements... (continued on page four)

Upcoming Medical Grand Rounds

May 5 “Bone Marrow-Derived Stem Cells in the Replacement of Damaged Airway Epithelium”
Alan Fine, MD
Associate Professor; Section of Pulmonary, Allergy and Critical Care Medicine, Boston University School of Medicine

May 12 SHAIA MEMORIAL FUND LECTURE
“Physicians and Pharma The New Ethics of Engagement in Clinical Practice”
Dr. Sheldon Krimsky, MD
Professor of Urban and Environmental Policy and Planning at Tufts University School of Urban and Environmental Policy and Planning in Boston, Mass., and Co-Director of the Urban and Environmental Policy Institute at Tufts University.

May 19 Annual Housesstaff Award Ceremony
Organized by the Internal Medicine Office of Educational Affairs

May 26 ANNUAL WILLIAM BLACKARD LECTURE
Organized by the Division of Endocrinology and Metabolism
"Polycystic Ovary Syndrome and Insulin Resistance: A Research Travelogue”
John E. Nestler, MD

Grand rounds are held at 12:00 noon in the Medical Sciences Building Auditorium. The calendar is subject to change.

NEWS BRIEFS

Dr. Kenneth Ellenbogen has been selected as an Elite Reviewer for the Journal of the American College of Cardiology.

Dr. Ron Clark received the following letter:

"Dr. Fowler, Dr. Kuey, Dr. Sheppard, Dr. Dugger and those working alongside have shown... that they are the top in their dedication and knowledge in their fields. Their passion for work is a testament to the quality that MCV Hospitals’ reputation (which we have learned about and will be spreading) supports.”

Dr. Peter Bøling received the following letter:

"There are few people walking around who have done more for my mother, or whom she respects more than you. Long before the House Calls’ staff blessed her, she began to hang on your every word and trust your medical advice... Her enrollment in House Calls truly blessed my mother’s life and mine as her full-time caregiver..."
of people figure skating, doing yoga, and playing guitars comfortably on their couches. Both drugs caught on big time, selling better than drugs for erectile dysfunction (go figure!). The potential cardiac risk could be negated by concommitant low-dose aspirin, couldn’t it? But wouldn’t this negate the GI protective benefit?

Events of the past few months in particular have not answered any of the questions, but things have become simpler. As the coxibs were studied for their potential in preventing colon cancer and Alzheimer’s disease, a clear cardiovascular risk was demonstrated again with rofecoxib and for the first time with celecoxib (in higher doses). A newer agent (valdecoxib) increased time with celecoxib (in higher doses). Again with rofecoxib and for the first time cardiovascular risk was demonstrated for their potential in preventing colon cancer and Alzheimer’s disease, a clear protective benefit?

In the end, we are still challenged to make NSAIDs less risky when we use them. Patients at low risk for GI complications should be treated with nonselective NSAIDs, and should have been all along. For patients with GI risk factors, concommitant proton-pump inhibitor (PPI) or misoprostil therapy should be used. Patients at low risk for GI complications should be treated with nonselective NSAIDs, and should have been all along. For patients with GI risk factors, concommitant proton-pump inhibitor (PPI) or misoprostil therapy reduce the ulcer risk in most studies, and celecoxib may not have much cardiovascular risk at lower doses. In addition, we really shouldn’t forget that there is always an alternative to an NSAID (e.g. low-dose steriod in RA, pure analgesics and local measures in osteoarthritis, tendinitis and bursitis).

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Although obese persons still have higher risk factor levels than lean persons, the levels of these risk factors are much lower than in previous decades.

—JAMA, 2005;293:1868–1874