Drug Monitor

NSAIDs and Colorectal Risk: The Other Side

It's been one of the biggest stories in health care in recent years: cutting the risk of colorectal cancer (CRC) by taking nonsteroidal anti-inflammatory drugs (NSAIDs). Both case-control and cohort studies have shown roughly a 40% reduction.

But a group of researchers from Harvard University and the Boston VA Health Care System, both in Boston, MA, take some issue with those findings. They note that several of the randomized trials were conducted in patients at high risk for CRC, such as those with a family history of adenomatous polyps. In other trials of apparently healthy men and women, daily aspirin had no effect on CRC risk, the researchers say.

They decided to analyze data from 22,044 healthy, male physicians enrolled in the Physicians' Health Study, which was designed to test the hypothesis that 325 mg of aspirin on alternate days would reduce the risk of cardiovascular disease and 50 mg of beta-carotene on alternate days would reduce the incidence of cancer (any type). The randomized treatment phase of the trial was intended to last for 20 years (ending in 1995), though the aspirin arm was halted early (after five years) because of the substantial reductions in cardiovascular risk observed. Following the randomized phase, the researchers continued to collect follow-up surveys from the participants until 2003.

During a median follow-up of 19 years, 495 physicians were diagnosed with CRC. In contrast to virtually all previous studies on risk of CRC, the researchers say they observed no substantial risk reduction. Regular use of any NSAID for five or more years was associated with a relative risk for CRC of 1.

The result was in line with their previous findings on randomized and postrandomized aspirin use in this study population, the researchers say, as well as with the Women's Health Study. They acknowledge, however, that the definition of regular NSAID use (more than 60 days of use per year) might have been too low to show a protective effect of these drugs on CRC risk. In addition, they say, the fact that study enrollment was limited to physicians with no clear indications or contraindications to regular NSAID use also might have affected the results.

Source: *Am J Med.* 2006;119:494–502.

Can Clozapine Cause Lupus?

Clozapine has an extensive safety profile, but it can have some significant adverse effects—possibly including drug-induced lupus (DIL). Researchers from Hadassah University Hospital and Hebrew University School of Medicine, Jerusalem, Israel report on a "classic case" of DIL in which clozapine was the likely culprit.

The patient, a woman with schizophrenia, was admitted to the hospital with a fever, myalgia, and weight loss of 3 kg. Her fever and myalgia, accompanied by arthralgia of the ankle and small joints of the hands, had developed three weeks earlier—just one week after clozapine initiation. A bone marrow biopsy showed hypercellularity with clusters of rich cytoplasm ("tissue paper") macrophages, findings usually associated with Gaucher disease, which the patient didn't have. A high turnover of granulocytes is a well known adverse effect of clozapine, the authors say. A test for antinuclear antibodies was strongly positive and showed the presence of antihistone antibodies—considered characteristic of DIL.

The patient's history included a previous occurrence of a lupus-like syndrome, which also had been attributed to clozapine use. These symptoms had appeared one year after clozapine initiation and had resolved within three months of drug discontinuation. Based on this history and her current condition, she was diagnosed with clozapine-induced lupus and the drug was once again withdrawn. All clinical symptoms and laboratory markers characteristic of DIL resolved shortly after clozapine withdrawal.

Unlike two previous reports of suspected clozapine-induced lupus, the researchers say their case was diagnosed using "strict" criteria for diagnosing systemic lupus erythematosus. In addition, the full remission of symptoms after drug discontinuation and the full-blown relapse after drug rechallenge lend strong support to the diagnosis.

The mechanisms of DIL have yet to be demonstrated conclusively. The researchers point out that while their patient's presentation resembled a hypersensitivity reaction, clozapine is associated with other, primarily cytotoxic adverse effects. They believe that several mechanisms, which might vary among different drugs, likely are involved in DIL development.

Source: *Ann Pharmacother.* 2006;40:983–985.

Ethnic Differences in ADRs

Research reports that include only vague summaries of data on adverse drug reactions (ADRs)—such as, "the drug was well tolerated"—may do a significant disservice to study patients who come from different

ethnic groups, charge researchers from City Hospital and University of Birmingham, both in Birmingham, England. In their meta-analysis of published research comparing ADRs of various cardiovascular drugs, they found that many studies failed to describe how ethnicity was classified; presented ADR data for only one treatment arm; or aggregated ADR data, making it difficult to determine how often specific ADRs were occurring and to whom.

A search of Medline and Embase through March 2005 revealed 132 studies (excluding case reports) related to cardiovascular therapy that incorporated descriptions of ethnicity and an ADR. Only 24, however, provided consistent data on ADRs for at least two ethnic groups. The results of these studies showed substantial differences with regard to ADRs and race.

In many of the studies, ADRs were more frequent among nonwhite patients—particularly black patients—than among white patients. For example, black patients were more likely to be affected by: angiotensin converting enzyme (ACE) inhibitor–induced angioedema, intracranial hemorrhage or moderate or severe bleeding after thrombolytic therapy, depression associated with hydrochlorothiazides, headache during antihypertensive therapy, and ibutilide-induced torsade de pointes. In addition, while taking digitalis, black patients had an increased risk of hospital admission for an associated adverse event, compared to white patients. And in another study, nonwhite race (black, Hispanic, or other) was a risk factor for hospital admission due to bleeding after oral anticoagulant treatment for deep vein thrombosis.

Two studies revealed that the risk of cough from ACE inhibitor treatment was three times as high among East Asian patients as it was among white patients. Another group of researchers found twice as many East Asian patients reported adverse effects with antihypertensive drugs, compared with white patients.

One large, open-label trial monitoring patients for 10 specific ADRs to the beta-adrenoceptor antagonist pindolol bucked the overall trend. In this study, white patients reported a greater number of each ADR than did black patients—though the differences were not significant.

The researchers performing the meta-analysis note that some of the genetic factors believed to affect response to drugs, such as cytochrome P450 genotype, are distributed differently in various ethnic groups. "When ethnic differences in susceptibility exist," the researchers say, "they may act as a marker for potentially important genetic or environmental factors that can influence the balance between benefit and harm." They suggest that increasing the recruitment of individuals from diverse ethnic groups and reporting data on ethnicity routinely and consistently could help improve comparisons between study findings.

Source: *BMJ*, doi:10.1136/bmj.38803.528113.55 (published May 5 2006).

IV Epinephrine to Treat Severe Asthma?

Is there a wider role for IV epinephrine in treating severe asthma in the emergency department (ED)? Yes, say Australian researchers from Western Health, Putland; the Joseph Epstein Centre for Emergency Medicine Research, Kerr, Kelly; and the University of Melbourne, Victoria. Moreover, they assert that adverse effects from epinephrine aren't a reason not to use the drug.

The researchers retrospectively reviewed data on all patients aged 18 to 55 who had a confirmed diagnosis of asthma; presented to the ED of one hospital between July 1998 and November 2003; were triaged as Austrailasian Triage Scale category 1, 2, or 3 (severe asthma); and were treated with IV epinephrine. (In Australia, inhaled albuterol is the standard treatment for mild to moderate asthma, with IV agents reserved for severe attacks.) Among the 220 cases, the average infusion rate was 1.5 µg/min, with total doses ranging from 15 to 99,551 µg. Infusions lasted from 10 minutes to 11.4 days.

In 67 episodes of IV epinephrine use, the researchers found 88 adverse events (AEs), resulting in a 30.5% AE rate per episode. Most of the recorded AEs were minor, however, such as uncomplicated sinus tachycardia or hypertension (23 and 30 cases, respectively). Of note, the researchers say they found no clinically significant consequences in any of the hypertensive episodes.

Only 3.6% of AEs were serious. Two patients had myocardial iscehmia, two had nonsinus tachyarrhythmia, and four had hypotension. No patients died. Three of the cases of hypotension required treatment and were related to sedation for endotracheal intubation. Of the 10 events that required IV epinephrine discontinuation, five were due to extravasation of drug or blanching around an IV site—but four occurred in one patient alone.

Even with the small number of serious AEs found in their review, the researchers say they may well have overestimated those actually caused by epinephrine. Some AEs might have been related to concurrent therapy, disease severity, or comorbidities. As long as AEs are not a concern, the researchers say there's a good rationale for using IV epinephrine rather than albuterol: Because it has alpha- and beta-agonist effects, it can address both airway resistance and airway edema. ●

Source: *Ann Emerg Med.* 2006;47:559–563.