NSAIDs Plus Low-Dose Aspirin Raise GI Bleeding Risk Substantially

BY BRUCE JANCIN
Denver Bureau

HONOLULU — Even over-the-counter doses of nonselective NSAIDs significantly increase the risk of serious GI complications, Joseph Biskupiak, Ph.D., said at the annual meeting of the American College of Gastroenterology.

Moreover, his study of a large, national outpatient primary care database of electronic medical records showed that this risk is further intensified by concomitant use of low-dose aspirin, added Dr. Biskupiak of the University of Utah College of Pharmacy, Salt Lake City.

"There are a couple of take-home messages here for the patient and physician populations. It's that [over-the-counter] NSAIDs are not benign. As physicians, you need to assess patient usage of these medications and inform them of the associated risks. And patients taking these medications need to discuss their use with their physician," he said.

Dr. Biskupiak reviewed the 3.2-million-patient GE Medical Systems Centricity database and identified 11,957 individuals taking OTC naproxen at 220 mg/day and 38,507 taking OTC ibuprofen at 200 mg/day who were free of medical conditions or therapies that would predispose to GI bleeding. He compared the incidence of GI perforations, ulcers, or bleeding (PUB) during the first 3 months after taking the NSAID—even a single dose—with the rates during the 6- and 12-month periods prior to taking either NSAID.

In the 6 months prior to taking ibuprofen, 55 patients experienced a PUB, as did 100 in the year prior to taking the drug. During the 3 months after starting on ibuprofen, patients were 2.5 times more likely to experience a PUB than in the previous 6 months, and 38% more likely to experience a PUB than in the year prior to taking the NSAID.

Over-the-counter NSAIDs are not benign. Patients taking them need to be informed of the associated risks.

DR. BISKUPIAK

Similarly, patients who took naproxen were 2.74 times more likely to develop PUBs than in the 6 months before taking the drug, and 54% more likely than in the year beforehand, he continued.

Concurrent low-dose aspirin was used by 2,328 patients who took naproxen; their risk of developing a PUB was twice that of patients on naproxen alone. The 4,843 patients on low-dose aspirin and ibuprofen were 3.36 times more likely to develop a PUB within 3 months of starting the NSAID than patients taking ibuprofen alone.

Session cochair Dr. David Y. Graham questioned the clinical relevance of Dr. Biskupiak's findings.

"The actual PUB complication rates with [over-the-counter] NSAIDs were maybe 1 in 200 patients per year. In the control group, it would be a little less than that. That's an extraordinarily low number. The question is, is it clinically important?" asked Dr. Graham, professor of medicine at Baylor College of Medicine, Houston.

Dr. Biskupiak's answer was emphatically yes.

"Considering that we're talking about an estimated 60 million Americans using OTC pain medications daily—many of whom are unaware that NSAIDs can cause major GI problems—even though 1 in 200 is a very small number, it turns out to be a significant total number of people," noted Dr. Biskupiak.

"And remember: More than 100,000 hospitalizations annually—as well as 16,000 deaths annually—are attributed to GI complications of NSAID usage. So I would say that there is a problem," the pharmacology researcher added.

His study was funded by Pfizer Inc. ■

Response to PPI Not Clear After First Week

COPENHAGEN — Some patients with dyspepsia not caused by reflux or a peptic ulcer who don't respond to a proton-pump inhibitor during the first week of treatment will respond after a few more weeks, based on results from two studies.

The first week on a proton-pump inhibitor (PPI) "is only moderately useful for predicting responses after 4 and 8 weeks of treatment," Dr. Sander Veldhuyzen van Zanten said at the 13th United European Gastroenterology Week. "It therefore makes sense to treat for 4-8 weeks" to see if the patient will respond.

Also, "the data clearly show that in a primary care setting, unless a patient has alarming symptoms, there's no reason to start with a double dose of a PPI," said Dr. van Zanten, a gastroenterologist and professor of medicine at Dalhousie University, Halifax, N.S.

One of the studies enrolled 1,250 patients, aged 18-50, who had epigastric pain or burning for at least 3 months, were negative for *Helicobacter pylori*, and had not been investigated by endoscopy. The study excluded patients whose predominant symptom was heartburn or acid regurgitation and those with more than one episode of heartburn or acid regurgitation per week.

Patients were randomized to start with 40 mg of esomeprazole once or twice daily for 1 week. About 44% of patients responded to both regimens, with no difference between the two groups. After the initial week, patients were rerandomized to continue on 40 mg of esomeprazole once daily or placebo for 7 more weeks. The full 8 weeks were completed by 1,084 patients.

Of the 716 patients who were on esomeprazole for 8 weeks, 339 patients (47%) responded. Among the 339 responders, 198 also had responded after 1 week but 141 patients (42% of all responders) had not shown any response during the first week of treatment.

Similar results were seen in a second study that enrolled 1,589 patients. The design of the second study was generally similar to the first, and 743 patients received esomeprazole treatment for 8 weeks. The 295 patients who responded after 8 weeks included 158 patients (54% of all responders) who had not responded during the first week of treatment.

The studies were sponsored by AstraZeneca, which markets esomeprazole (Nexium).

—Mitchel L. Zoler

CLINICAL CAPSULES

Itopride for Functional Dyspepsia

For patients with functional dyspepsia, treatment with itopride for 8 weeks provides a significantly greater reduction in symptoms than does placebo, according to results from a recent randomized trial.

Itopride is a dopamine D2 antagonist that inhibits acetylcholinesterase activity. In Japan, the drug is often prescribed for functional dyspepsia, even though it had not been evaluated in randomized, controlled trials.

In the current study, Dr. Gerald Holtmann of the University of Adelaide (Australia) and his associates randomized 554 patients with functional dyspepsia to receive itopride at 50 mg, 100 mg, or 200 mg three times daily or placebo (N. Engl. J. Med. 2006;354:832-40).

After 8 weeks, the overall response rate, defined by the patient's global assessment of efficacy, was significantly greater with itopride than with placebo (60% vs 41%). This was a dose-dependent effect, with response rates of 57% at 50 mg, 59% at 100 mg, and 64% at 200 mg.

The incidence of adverse events was similar for itopride (38%) and placebo (37%). Although prolactin levels increased significantly in the 100-mg and 200-mg itopride groups, no related clinical signs or symptoms were noted.

COX-2 Inhibitors in IBD Patients

Patients with ulcerative colitis in remission who had a history of nonspecific arthritis, arthralgia, or another condition treatable with NSAID therapy did not have a greater relapse rate with the use of celecoxib for up to 14 days than with placebo, Dr. William J. Sandborn and his colleagues reported.

In a double-blind, pilot trial, 221 patients were randomized to receive oral celecoxib 200 mg or placebo twice daily for 14 days. Ulcerative colitis (UC) exacerbation occurred in 3 of 110 evaluated patients on celecoxib and in 4 of 107 on placebo (Clin. Gastroenterol. Hepatol. 2006;4:203-11). The study was supported by a research grant from Pfizer Inc.

In a second study, Dr. Ken Takeuchi and his colleagues studied patients with quiescent Crohn's disease or UC. First, they randomized 109 patients to 4 weeks of treatment with either acetaminophen or a conventional NSAID (naproxen, diclofenac, or indomethacin). Of patients taking NSAIDs, 17%-28% had a relapse; whereas no patients taking acetaminophen relapsed (Clin. Gastroenterol. Hepatol. 2006;4:196-202).

None of the 100 patients in the second part of the study had an early relapse on acetaminophen, low-dose aspirin (selective COX-1 inhibitor), or nimesulide (selective COX-2 inhibitor not available in the United States). Those on naproxen (topical COX-1 and -2 inhibitor) or nabumetone (COX-1 and -2 inhibitor) had relapses associated with intestinal inflammation. The research was funded in part by grants from Merck Sharp & Dohme and Helsinn Pharmaceuticals, manufacturer of nimesulide.

The studies "indicate that nonselective inhibitors carry a significant risk for exacerbating IBD whereas celecoxib is safe for 2 weeks for patients in remission. Low-dose aspirin use remains in a gray zone of uncertain but probable safety," said Dr. Joshua R. Korzenik and Dr. Daniel K. Podolsky of Harvard Medical School, Boston, in an editorial (Clin. Gastroenterol. Hepatol. 2006;4:157-9).

Treatment Options for Pancreatitis

Surgical drainage of the pancreatic duct was more effective for relieving pain than endoscopic drainage in a study of 39 patients with chronic pancreatitis.

"Surgery is safe and required fewer therapeutic interventions," Dr. Djuna L. Cahen said at the 13th United European Gastroenterology Week. Surgery also led to faster pain relief, said Dr. Cahen, a gastroenterologist at the University of Amsterdam Academic Medical Center.

The study involved all patients referred to the Academic Medical Center from January 2000 to October 2004 with symptomatic, chronic pancreatitis and a dominant pancreatic duct obstruction caused by strictures or stones.

Of the 39 patients, 20 were randomized to surgical drainage by pancreaticojejunostomy and 19 underwent endoscopic drainage by stent insertion. Endoscopic treatment was preceded by extracorporeal shock wave lithotripsy in 16 patients who had stones causing the obstruction.

The study's primary end point was the average Izbicki pain score during a median follow-up of 24 months. The average pain score was 25 in the surgery group and 51 in the endoscopy group, a statistically significant difference.

Clinical success—defined as a reduction in the pain score of at least 50% from baseline to the end of follow-up—was achieved in 32% of endoscopy patients and 75% of surgery patients. The two groups did not differ in terms of complications, morbidity, mortality, or hospital length of stay.

—From staff reports