PPI Use, Fracture Risk Tied to Other Risk Factors

BY DENISE NAPOLI

FROM THE JOURNAL GASTROENTEROLOGY

Hip fracture patients were 30% more likely to have a long-term history of proton pump inhibitor use, compared with controls, Dr. Douglas A. Corley and his colleagues reported.

Moreover, the association was found to be stronger with higher doses of PPIs, and the link diminished after PPI discontinuation, the researchers wrote.

"These findings do not recommend against acid suppression for persons with clear indications for treatment," wrote Dr. Corley, a researcher with Kaiser Permanente Northern California (Gastroenterology July [doi: 10.1053/j.gastro.2010.03.055]). However, "they do advise appropriate vigilance in prescribing these medications to persons with defined indications and at the lowest effective dose."

Dr. Corley and his colleagues looked at 33,752 adult members of the Kaiser Permanente Northern California integrated health care delivery system who had an incident diagnosis of a hip fracture between January 1995 and September 2007. To be included in the study, patients had to have been in the Kaiser Permanente Northern California system for at least 2 years prior to their fracture. Patients who had a previous hip or femur fracture diagnosis were excluded.

Patients were roughly matched in a 4:1 ratio with demographically comparable controls, also from the Kaiser Permanente Northern California system. Controls had no history of hip fracture, and had also been in the Kaiser system for at least 2 years.

Patients were predominantly women (65.7%), 70 years of age or older (69.4%), and white (79.6%), according to the authors. Roughly 40% had received a prescription for a proton pump inhibitor while in the Kaiser Permanente Northern California system.

According to Dr. Corley, patients whose records indicated "long-term" use of PPIs (defined by the authors as greater than 2 years) had an odds ratio of having a fracture within the study period of 1.30, compared with nonusers (95% confidence interval, 1.21-1.39).

However, all of the increased risk for fracture was present only in patients who had at least one other risk factor for fracture, such as smoking, dementia, arthritis, or visual impairment. Indeed, among patients with none of these risk factors, the odds ratio for fracture among PPI users was 0.66 (95% CI, 0.38-1.12).

The researchers also found a trend toward increased fracture risk among subjects taking higher daily doses of PPIs. For example, among patients taking an average of 0.01-0.74 pills/day, for a duration between 2 and 3.9 years, the OR for a fracture, compared with nonusers, was 1.23 (95% CI, 1.08-1.39); among users taking 0.75-1.49 pills/day, for the same duration of time, the OR was 1.43 (95% CI, 1.28-1.60), and for more than 1.49 pills/day the OR was 1.41 (95% CI, 1.21-1.64).

Despite the association with PPI dosage, there was no link between duration of PPI use and fracture risk.

The researchers also found that "the strength of the association between PPI use and hip fracture was greatest among current users and diminished after discontinuation of PPI use." For example, while the OR for current users was 1.30 (95% CI, 1.21-1.41), it was 1.24 for patients whose most recent prescription was 1.0-1.9 years before the index date (95% CI, 0.90-1.72), and dropped to 1.09 for patients whose last PPI prescription was 2.0-2.9 years before the index date (95% CI, 0.64-1.85).

Dr. Corley proposed several mechanisms by which acid inhibition could influence fracture risk. For one, he said, acid inhibition could directly influence calcium absorption: he pointed to a small, randomized trial in which omeprazole decreased the absorption of radio-labeled calcium pills by 61%, compared with placebo (Am. J. Med. 2005;118:778-81).

"Second," he wrote, "acid inhibition may induce hyperparathyroidism, which directly decreases bone mineral density, through hypergastrinemia, although this is controversial."

Finally, he suggested that fracture risk may be mediated by interference by PPIs with bone remodeling. However, he added, "none of these mechanisms are proven."

Fracture risk also was increased in patients using histamine$_2$-receptor antagonists, another class of drugs that inhibit acid secretion (OR, 1.18).

The authors concluded that acid inhibition might raise fracture risk in persons already at risk for osteoporosis, although confounding cannot be excluded. ■

VITALS

Major Finding: Among patients taking proton pump inhibitors for at least 2 years, the risk of having a hip fracture was increased by 30%, but only when at least one other fracture risk factor (smoking, dementia, arthritis, visual impairment) was present. Among PPI users with none of these other risk factors, the odds ratio for fracture was 0.66.

Data Source: A nested case-control study using data from an integrated health services organization, including 33,752 cases and 130,471 controls.

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PPI-Associated Adverse Effects Are Overstated, Expert Says

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — Adverse effects attributed to proton pump inhibitors, including a risk for adverse interactions with clopidogrel, have probably been overstated.

Dr. Michael F. Vaezi, professor of medicine and clinical director of the division of gastroenterology at Vanderbilt University Medical Center in Nashville, Tenn., told attendees that although there are "interesting epidemiologic associations" that may have "some biologic plausibility," the associations are weak in magnitude and are based on inconsistent findings from heterogeneous studies with a high potential for confounding.

Issues With Clopidogrel

The potential for an interaction with clopidogrel—that is, whether PPIs (specifically, omeprazole and esomeprazole) inhibit the anticoagulation effect of clopidogrel so that it is less effective in preventing cardiovascular injury—has been a "huge issue," because cardiologists, or patients themselves, are discontinuing proton pump inhibitors (PPIs) that they were using for reflux disease.

A number of studies have suggested harmful interactions, Dr. Vaezi said. One study showed a reduction in the platelet reactivity index, indicating poor response to clopidogrel, in 61% of patients who received omeprazole vs. 26% of patients in a placebo group, a highly significant difference (J. Am. Coll. Cardiol. 2008;51:256-60). In a retrospective Department of Veterans Affairs cohort study, all-cause mortality was significantly increased in patients on PPIs plus clopidogrel vs. clopidogrel alone (JAMA 2009;301:937-44).

But a recent meta-analysis of 23 studies on this topic, involving 93,278 patients, showed no excess risk for cardiovascular events for PPIs that were used with clopidogrel in observational studies (odds ratio, 1.15) among propensity-matched or randomized-trial participants (Aliment. Pharmacol. Ther. 2010;31:810-23). No significant association was found between PPI use and overall mortality, noted Dr. Vaezi.

"The most recent analysis asked the right question: If you are not on a PPI but are on clopidogrel, what is the risk of bleeding?" he said. A recent study examined a database of more than 20,000 patients (including 7,593 concurrent users of clopidogrel and PPIs) who were hospitalized for gastroduodenal bleeding and serious cardiovascular disease (Ann. Intern. Med. 2010;152:337-45). The adjusted incidence of hospitalization for bleeding in concurrent users was 50% lower than it was in nonusers of PPIs who were taking clopidogrel. For patients at highest risk for bleeding, PPI use was associated with an absolute reduction of 28.5 per 1,000 person-years, the study found.

The authors concluded that in patients with serious coronary heart disease that was treated with clopidogrel, concurrent PPI use was associated with reduced hospitalizations for gastroduodenal bleeding, and the corresponding point estimate for serious cardiovascular disease was not increased.

"But we are left with the [Food and Drug Administration] warnings about using omeprazole and esomeprazole, though the data are not strong," Dr. Vaezi maintained. In his practice, he keeps patients on omeprazole and clopidogrel and prefers not to switch to another PPI, having observed that some such patients stop responding to PPIs altogether. It may be prudent, however, to give one drug at night and the other in the morning, he added.

Hip Fracture

PPIs have been associated with a risk for hip fracture, but a nested, case-control study from the U.K. General Practice Research Database, including 13,556 cases and 135,386 controls, showed an odds ratio of approximately 2.0 in the crude analysis, and approximately 1.5 in the adjusted analysis (JAMA 2006;296:2947-53). However, when others analyzed this study and excluded patients with baseline risk factors for fracture, they observed no increased risk among PPI users (Pharmacotherapy 2008;28:951-9).

"If anything, patients who were on PPIs the longest were somewhat protected," Dr. Vaezi noted. He added that other studies have found that the extended use of PPIs, and also use of H_2 receptor blockers, is associated with reduced risk—which are interesting findings that are inconsistent with the concept of harm from PPIs, he maintained. However, despite the negative association the FDA most recently has decided to revise the warnings and precautions section of the prescription labeling as well as the OTC drug facts label for proton pump inhibitors to warn about the potential increased risk of fractures of hip, wrist and spine.

The most recent study, based on the Manitoba Bone Mineral Density Database, showed that 5 years of PPI use posed no risk for adverse effects to the hip or spine (Gastroenterology 2010;138:896-904), he said. Analyses of associations with pneumonia and anemia also point to weak effects, he added. ■

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