PPI Therapy, Fracture Risk Link Raises Concerns

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Contributing Writer

Hip fracture risk was increased with long-term use of proton pump inhibitors in a study published recently in the Journal of the American Medical Association, and the findings have led to concerns and questions among both gastroenterologists and patients who take these frequently prescribed drugs.

Dr. Yu-Xiao Yang of the division of gastroenterology at the University of Pennsylvania and his colleagues analyzed data on 1.8 million patients in the General Practice Research Database, a national database of patients in the United Kingdom, to assess a possible association between proton pump inhibitor (PPI) therapy and the risk of hip fracture (JAMA 2006;296:2947-53).

The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI use was significantly increased at 1.44 (95% confidence interval [CI], 1.30-1.59; *P* less than .001). In addition, patients who were prescribed long-term, high-dose PPI therapy had a markedly increased risk of hip fracture, with an AOR of 2.65 (95% CI, 1.80-3.90; *P* less than .001).

Clinicians who are concerned about the hip fracture risk in patients who may not need to take a PPI continually could discontinue the drug and see how the patient fares.

Dr. Colin W. Howden, professor of gastroenterology at Northwestern University in Chicago, said the study does indicate that PPIs increase the risk of hip fracture, but he urged physicians and patients to avoid becoming overly concerned about the findings. "The risk needs to be put in context," he said.

All patients were at least 50 years old and had no documented hip fracture before the study started or during the first year of follow-up; all started follow-up between May 1987 and March 2003. The cohort included 192,028 people who had received at least one prescription for a PPI during the follow-up period; 187,686 people who received at least one prescription for a histamine$_2$ receptor antagonist (H_2RA) during the follow-up period but had not used a PPI; and 1.4 million people who had no documented use of either a PPI or H_2RA, and were thus classified as acid-suppression nonusers.

The authors matched cases of those who had a hip fracture during the study period with controls who did not have a hip fracture. Cases and matched controls (up to 10 controls for each case) were similar in terms of sex, year of birth, and both the calendar period and the duration of follow-up before the index date.

The results revealed that 13,556 incident hip fractures—10,834 among acid suppression nonusers and 2,722 among PPI users—occurred during the study period. These hip fracture cases were matched with a total of 135,386 controls (at least one control per case).

In addition to the increased adjusted odds ratio for hip fracture after more than 1 year of PPI use, the data also showed that the strength of the association between hip fracture and PPI use increased with each cumulative year of use. The AOR was 1.22 for 1 year of PPI therapy (95% CI, 1.15-1.30), 1.41 for 2 years (95% CI, 1.28-1.56), 1.54 for 3 years (95% CI, 1.37-1.73), and 1.59 for 4 years (95% CI, 1.39-1.80), with *P* less than .001 for all comparisons.

Dr. Howden commented that this study should remind physicians to review their patients' medication lists, particularly those of older patients who are at higher risk for hip fractures. "The bottom line is that if [patients need] to be on a PPI for a valid reason, they should be on a PPI," he said.

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The study did not determine the mechanism behind the increased risk of hip fracture in PPI users, but the authors noted that these drugs may decrease calcium

absorption via induction of hypochlorhydria, and may also reduce bone resorption by inhibiting the osteoclastic proton transport system.

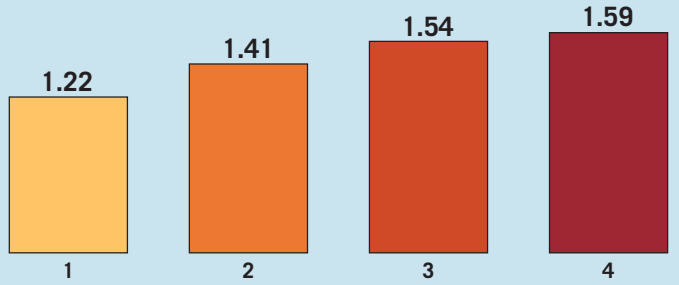
Currently, there are no guidelines for intensifying osteoporosis screening in patients who are taking long-term PPI therapy or for initiating drug therapy to counteract osteoporosis in this patient population.

Until specific guidelines are published, physicians should consider the needs of individual patients and make diagnostic and treatment recommendations accordingly. Dr. Howden cautions against taking an alarmist approach to this study.

"I think the absolute risk is quite small, but it's not zero," he said.

Dr. George Sachs, professor of medicine and physiology at the University of California, Los Angeles, agrees that the study shows only a small excess risk of hip fracture in the group taking PPIs. These medications have only a small effect on stomach pH levels and hence calcium absorption, according to Dr. Sachs. Increasing calcium supplements or milk intake is the best method of decreasing the risk of hip fracture. "I think if [doctors] have concerns, they can always tell their patients to take extra calcium," he said. ■

Hip Fracture Risk Linked to Duration of PPI Therapy



Note: Adjusted odds ratios based on an analysis of 1.8 million patients in the United Kingdom's General Practice Research Database.

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