CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Proton Pump Inhibitors and Risk of Fractures: A Meta-Analysis of 11 International Studies

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ABSTRACT

BACKGROUND: Concerns have been raised about the risk of fractures with acid-suppressive medications, such as proton pump inhibitors and histamine$_2$-receptor antagonists.

METHODS: This meta-analysis evaluated the association between proton pump inhibitor or histamine$_2$-receptor antagonist use and fractures. We performed a systematic search of published literature (1970 to October 10, 2010) in MEDLINE, EMBASE, and other sources. Ten publications reporting 11 studies were considered eligible for analysis.

RESULTS: All studies were observational case-control or cohort studies and primarily evaluated older adults. The summary effect estimate for risk of hip fracture increased modestly among individuals taking proton pump inhibitors (relative risk [RR] 1.30, 95% confidence interval [CI], 1.19-1.43). There also was an increase in spine (RR 1.56, 95% CI, 1.31-1.85) and any-site fractures (RR 1.16, 95% CI, 1.04-1.30) among proton pump inhibitor users. These findings were similar in both men and women and after stratification by duration of use. In contrast, histamine$_2$-receptor antagonist use was not significantly associated with increased risk of hip fracture (RR 1.12, 95% CI, 0.97-1.30).

CONCLUSION: In this meta-analysis of observational studies, proton pump inhibitors modestly increased the risk of hip, spine, and any-site fractures, whereas histamine$_2$-receptor antagonists were not associated with fracture risk. The possibility of residual confounding cannot be excluded. Further skeletal evaluation should be considered for patients who are taking proton pump inhibitors and also at risk for osteoporotic fracture.

 • *The American Journal of Medicine (2011) 124, 519-526*

KEYWORDS: Bone mineral density; Calcium absorption; Fracture; H2-receptor antagonists; Osteoporosis; Proton pump inhibitor

Proton pump inhibitors are potent acid-suppressive medications commonly used for management of acid-related diseases, such as gastroesophageal reflux disease. Since their first introduction in 1989, proton pump inhibitors have become the third-highest prescription drug seller in the United States, garnering $13.6 billion in 2009.[1] Histamine$_2$-receptor antagonists are an older class of acid-suppressive medication that have a weaker acid suppressive effect than proton pump inhibitors. Long-term therapy with these medications is increasingly common.[2]

In recent years, concerns have been raised about the long-term safety profile of acid-suppressive medications, including potential adverse effects such as increased risk of respiratory and enteric infections,[3-5] nutritional deficiencies,[6,7] and bone fractures.[8-12] The Food and Drug Administration (FDA) recently published an advisory (updated March 23, 2011) communicating the possible increased risk of fractures with the use of high dose and/or long-term proton pump inhibitors.[13]

The FDA recommendations were based on several epidemiologic studies that have suggested an association between proton pump inhibitor use and hip, wrist, and spine

Funding: Dr Bauer is supported by National Institutes of Health Grant K24 ARO51895.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2011.01.007

fractures.[8-12,14,15] However, not all studies demonstrate a significant association,[14,15] and no consensus exists about the true magnitude of this risk. Further data have been published on this topic that may not have been reviewed in the FDA advisory.[16-20] We quantitatively synthesized all the currently available data in a meta-analysis to estimate the overall effect of proton pump inhibitor use on fracture rates.

CLINICAL SIGNIFICANCE

- There has been recent concern that proton pump inhibitors and histamine$_2$-receptor antagonists may be associated with fractures.
- In this meta-analysis of 11 observational studies, proton pump inhibitors modestly increased the risk of hip, spine, and any-site fractures.
- Histamine$_2$-receptor antagonists were not associated with fracture risk.
- Further skeletal evaluation should be considered for patients who are taking proton pump inhibitors and also at risk for osteoporotic fracture.

MATERIALS AND METHODS

Eligibility Criteria

Methods of the analysis were prespecified in a protocol. To be eligible, studies had to examine the risk of bone fracture attributable to the use of proton pump inhibitors or histamine$_2$-receptor antagonists, and include a comparator control group. Medication use had to be documented before occurrence of fracture. Analyses had to be adjusted at minimum for age and gender.

Search Strategy

PubMed/MEDLINE (National Center for Biotechnology Information), EMBASE (Elsevier), Web of Science (ISI Web of Knowledge), and BIOSIS Previews (ISI Web of Knowledge) were searched from 1970 to October 10, 2010, using terms for fractures and for proton pump inhibitors or histamine$_2$-receptor antagonists. The search strategy (Supplemental Table 1 online) was carried out by a librarian (PB). No language limits or methodology filters were applied. Programs from the annual meetings of the Endocrine Society (1996-2009) and the American Association of Clinical Endocrinologists (2002-2010) were hand-searched. Programs from the annual meetings of the American Society for Bone and Mineral Research, the American Gastroenterological Association, and the American College of Gastroenterology were included in the material searched through BIOSIS Previews. Reference lists of reviews identified in the search were scanned for candidate studies.

Data Collection

Eligibility assessment was performed independently by 2 investigators (EY and DB). Discrepancies were resolved by discussion between the 2 reviewers; if no agreement could be reached, a third author would decide. Quality assessments were based on adjustment for confounding. When effect estimates were reported for more than 1 set of adjustments, we selected the most adjusted estimate. We contacted 8 authors; all of whom provided additional unpublished data for fracture risk by sites and sub-analyses restricted by duration of medication use.

Definition of Exposure

The majority of studies defined proton pump inhibitor or histamine$_2$-receptor antagonist exposure as current or recent medication use assessed by prospective questioning of subjects[10,14,16,21] or review of prescription databases.[9,11,18] Three studies defined exposure on the basis of cumulative medication use from prescription databases, regardless of exposure timing.[8,12,20] Multiple studies examined dose and duration effects,[8,9,11,12,14,18,20] but incompatible definitions precluded overall pooling of dose-effects.

Definition of Outcomes

The predefined primary end point was hip fracture, which was assessed prospectively by self-report and confirmed radiologically[10,14,16,21] or by retrospective review of administrative databases.[8,9,11,12,18,20] Secondary end points included any-site fractures and spine fractures. For this meta-analysis, the following definitions of any-site fractures were combined: any clinical fracture,[9] clinical osteoporotic fractures,[11,14,19] or clinical non-spine fractures.[10] Clinical spine fractures[9,14] and morphometric spine fractures[16] also were analyzed together for this meta-analysis.

Statistical Analysis

Relative risks (RRs) and odds ratios were log-transformed and used interchangeably as measures of association because fracture is a rare event, and most case-control studies used an open-cohort sampling design. Effect estimates were pooled via DerSimonian and Laird random-effects models.[22] Stratified analyses were conducted to determine whether differences in gender, fracture site, study design, or duration of medication use identified important subgroups or explained heterogeneity across studies.[23] The I^2 statistic was used to determine the percentage of total variability due to heterogeneity rather than chance.[24] We used Begg's and Egger's tests to assess potential publication bias and evaluated the symmetry of individual study estimates around the pooled estimate using Begg funnel plots.[25] All analyses were conducted using STATA 13 (StataCorp, College Station, Tex); *P* values less than .05 were considered statistically significant.

RESULTS

Study Selection

The systematic search of MEDLINE, EMBASE, and other sources provided a total of 642 citations, after adjusting for duplicates. Of these, 573 were excluded after initial ab-