

## Risk of fracture and pneumonia from acid suppressive drugs

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### Abstract

A recently published systematic review and meta-analysis, incorporating all relevant studies on the association of acid suppressive medications and pneumonia identified up to August 2009, revealed that for every 200 patients, treated with acid suppressive medication, one will develop pneumonia. They showed the overall risk of pneumonia was higher among people using proton pump inhibitors (PPIs) [adjusted odds ratio (OR) = 1.27, 95% CI: 1.11-1.46,  $I^2 = 90.5\%$ ] and Histamine-2 receptor antagonists (H<sub>2</sub>RAs) (adjusted OR = 1.22, 95% CI: 1.09-1.36,  $I^2 = 0.0\%$ ). In the randomized controlled trials, use of H<sub>2</sub>RAs was associated with an elevated risk of hospital-acquired pneumonia (relative risk 1.22, 95% CI: 1.01-1.48,  $I^2 = 30.6\%$ ). Another meta-analysis of 11 studies published between 1997 and 2011 found that PPIs, which reduce stomach acid production, were associated with increased risk of fracture. The pooled OR for fracture was 1.29 (95% CI: 1.18-1.41) with use of PPIs and 1.10 (95% CI: 0.99-1.23) with use of

H<sub>2</sub>RAs, when compared with non-use of the respective medications. Long-term use of PPIs increased the risk of any fracture (adjusted OR = 1.30, 95% CI: 1.15-1.48) and of hip fracture risk (adjusted OR = 1.34, 95% CI: 1.09-1.66), whereas long-term H<sub>2</sub>RA use was not significantly associated with fracture risk. Clinicians should carefully consider when deciding to prescribe acid-suppressive drugs, especially for patients who are already at risk for pneumonia and fracture. Since it is unnecessary to achieve an achlorhydric state in order to resolve symptoms, we recommend using the only minimum effective dose of drug required to achieve the desired therapeutic goals.

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**Key words:** Acid-suppressive drugs; Pneumonia; Fracture

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### INTRODUCTION

Recently, the medical literature has paid considerable attention to unrecognized adverse effects of commonly used medications and their potential public health impact<sup>[1,2]</sup>. Acid-suppressive drugs (ASDs), represent the second leading category of medication worldwide, with sales totalling US\$26.9 billion in 2005<sup>[3]</sup>. Experts have generally viewed proton pump inhibitors (PPIs) as safe<sup>[4]</sup>. However, potential complications such as gastrointestinal neoplasia, malabsorption of nutrients and increased susceptibility to infection and fracture have caused concern<sup>[5]</sup>.

Of special interest is the possibility that ASDs could increase susceptibility to respiratory infections because these drugs increase gastric pH, thus allowing bacterial colonization<sup>[6,7]</sup>. Several previous studies have shown that treatment with ASDs might be associated with an increased risk of respiratory tract infections<sup>[8]</sup> and community-acquired pneumonia in adults<sup>[6,7]</sup> and children<sup>[9]</sup>. Given the widespread use of PPIs and Histamine-2 receptor antagonists (H<sub>2</sub>RAs), clarification of the potential impact of acid-suppressive therapy on the risk of pneumonia is of great importance to public health<sup>[10]</sup>.

Some findings have raised the possibility that PPIs may prevent osteoporosis and fractures. Several *in vitro* and animal studies have suggested that PPIs may decrease bone resorption by inhibiting osteoclastic vacuolar hydrogen potassium adenosine triphosphatase (H<sup>+</sup>/K<sup>+</sup> ATPase) activity<sup>[11-15]</sup>. Osteoclasts possess proton pumps, which are used during the excretion of H<sup>+</sup> ions for bone resorption. Osteoclast-selective PPIs may therefore be used as antiresorptive agents<sup>[16]</sup> with the potential of preventing fractures<sup>[17-20]</sup>. Administration of a selective inhibitor of the osteoclastic vacuolar H<sup>+</sup>/K<sup>+</sup> ATPase prevents bone loss in ovariectomized rats, an animal model representative of postmenopausal osteoporosis<sup>[19]</sup>. However, as bone resorption is necessary for the development of normal bone microstructure, one may speculate that PPI-induced blockade of the osteoclast-associated vacuolar proton pump may actually increase fracture risk<sup>[21]</sup>.

## USE OF ACID-SUPPRESSIVE DRUGS AND RISK OF PNEUMONIA

A recently published systematic review and meta-analysis, which incorporated all relevant studies on the association of acid suppressive medications and pneumonia that could be identified to August 2009, showed that of every 200 inpatients treated with acid suppressive medication one will develop pneumonia. From a total of 2377 articles identified in the initial search for observational studies, the authors reviewed 60 abstracts and 18 full articles, including 8 of these articles in their final analysis. They identified 8513 randomized controlled trials, and reviewed 914 abstracts and 35 full articles, including 23 of articles and 2 bibliographies of relevant articles in the study. In summary, they included five case-control studies<sup>[6,7,10,22,23]</sup>, three cohort studies<sup>[3,24,25]</sup>, and 23 randomized controlled trials<sup>[26-48]</sup> in the final analysis.

### Main pooled analyses

Meta-analyses on observational studies with the two types of ASD showed significant positive associations between use of PPI and risk of pneumonia [adjusted odds ratio (OR) = 1.27, 95% CI: 1.11-1.46,  $I^2 = 90.5\%$ ] and between use of H<sub>2</sub>RA and risk of pneumonia (adjusted OR = 1.22, 95% CI: 1.09-1.36,  $I^2 = 0.0\%$ ). Meta-analysis of randomized controlled trials examining risk of hospital-acquired pneumonia in association with use of H<sub>2</sub>RA s confirmed

the findings of the observational studies (relative risk: 1.22, 95% CI: 1.01-1.48,  $I^2 = 30.6\%$ ).

### Subgroup meta-analyses

In subgroup analyses by type of pneumonia, a significant positive association was observed between use of PPIs and community-acquired pneumonia (adjusted OR = 1.34, 95% CI: 1.14-1.57,  $I^2 = 93.6\%$ ) and between use of H<sub>2</sub>RAs and hospital-acquired pneumonia (adjusted OR = 1.24, 95% CI: 1.05-1.47,  $I^2 = 0.0\%$ ). Subgroup analyses by dose indicated a dose-response relationship. A higher dose of PPIs was more strongly associated with pneumonia (adjusted OR = 1.52, 95% CI: 1.31-1.76,  $I^2 = 27.5\%$ ) than the usual dose (adjusted OR = 1.37, 95% CI: 1.08-1.74,  $I^2 = 86.5\%$ ).

Subgroup analyses by duration of exposure showed that the strength of the association between use of PPIs and risk of pneumonia decreased with longer duration of therapy before the index date (date of diagnosis of pneumonia). There were significant positive associations between risk of pneumonia and use of PPIs within 7 d before the index date (adjusted OR = 3.95, 95% CI: 2.86-5.45,  $I^2 = 0.0\%$ ), within 30 d before the index date (adjusted OR = 1.61, 95% CI: 1.46-1.78,  $I^2 = 30.6\%$ ) and from 30 to 180 d before the index date (adjusted OR = 1.36, 95% CI: 1.05-1.78,  $I^2 = 84.3\%$ ).

The risk of pneumonia was greater with the use of H<sub>2</sub>RAs within 7 d before the index date (adjusted OR = 5.21, 95% CI: 4.00-6.80,  $I^2$  not available). This risk also appeared greater with the use of these drugs within 30 d before the index date (adjusted OR = 1.49, 95% CI: 0.82-2.72,  $I^2 = 80.4\%$ ) and from 30 to 180 d (adjusted OR = 1.21, 95% CI: 0.94-1.56,  $I^2 = 27.6\%$ ), although these associations were not statistically significant.

Subgroup analyses of the 23 randomized controlled trials by comparators showed a significant positive association between use of H<sub>2</sub>RAs and risk of pneumonia in studies that employed sucralfate as a control (relative risk: 1.33, 95% CI: 1.04-1.69,  $I^2 = 24.7\%$ ). Placebo-controlled studies also indicated an overall increase in the risk of pneumonia with these drugs, but this increase was not statistically significant (relative risk: 1.09, 95% CI: 0.80-1.48,  $I^2 = 37.9\%$ ).

The authors conducted subgroup meta-analyses of the observational studies and randomized controlled trials according to methodological quality. Among the observational studies, they observed a significant positive association for both high-quality studies (adjusted OR = 1.29, 95% CI: 1.17-1.42,  $I^2 = 0.0\%$ ) and low-quality studies (adjusted OR = 1.15, 95% CI: 1.00-1.32,  $I^2 = 82.1\%$ ). Among the randomized controlled trials, the risk of pneumonia appeared greater in low-quality studies (relative risk: 1.35, 95% CI: 1.10-1.67,  $I^2 = 12.5\%$ ), whereas there was no effect among the high-quality studies (relative risk: 0.96, 95% CI: 0.65-1.43,  $I^2 = 47.0\%$ ).

### Discussion

Several lines of evidence point to the biological plausi-

bility of these observations. Firstly, ASDs may increase the risk of pneumonia by inhibiting the secretion of gastric acid, thus allowing bacterial overgrowth and colonization in the upper alimentary tract with subsequent translocation to the lungs by aspiration<sup>[6,7,49]</sup>. Secondly, H<sup>+</sup>/K<sup>+</sup> ATPase is present not only in the parietal cells of the stomach, but also in the respiratory tract<sup>[50,51]</sup>. It is conceivable that use of a PPI could alter the pH of the seromucinous secretions by inhibiting this enzyme, thereby encouraging bacterial growth in the respiratory tract, which could in turn lead to increased risk of pneumonia<sup>[5]</sup>. Thirdly, *in vitro* studies have shown that ASDs may impair the function of neutrophils and the activity of natural killer cells<sup>[52-58]</sup>.

Interestingly, the most striking increase in the risk of pneumonia in association with PPIs was observed in the first week of use. The risk of pneumonia associated with use of PPIs was attenuated, but still significant, between 30 and 180 d. Recipients of H<sub>2</sub>RAs between 30 and 180 d before the index date appeared to have an increased risk of pneumonia, although the association was not statistically significant. These findings might reflect tolerance<sup>[5]</sup>. Tolerance to H<sub>2</sub>RAs generally develops within 2 wk with repeated administration, resulting in a decline in acid suppression<sup>[59]</sup>. Another reason may be that those who are more susceptible to pneumonia become ill with this disease soon after starting ASDs, leaving fewer susceptible individuals among those using these drugs for longer periods. That is, patients who remain on the drug are those who can tolerate it, whereas those who are susceptible select themselves out of the population at risk. This depletion of susceptibility effect has been considered in other pharmacoepidemiologic studies of adverse events<sup>[60]</sup>.

## USE OF ACID-SUPPRESSIVE DRUGS AND RISK OF FRACTURE

A recently published meta-analysis found possible evidence linking PPI use to an increased risk of fracture, but no association between H<sub>2</sub>RA use and fracture risk. The widespread use of PPIs means that the potential risk of fracture is of great importance to public health. The authors excluded 170 duplicate articles and an additional 1621 articles that did not meet the selection criteria. They reviewed the full texts of the remaining 18 articles, eventually excluding 7 of them. The remaining 11 studies were included in the final analysis<sup>[61-67]</sup>.

### Main pooled analyses

The overall use of PPIs was associated with a significantly increased risk of any fracture in a random-effects model meta-analysis of 4 case-control studies, 3 nested case-control studies, and 3 cohort studies (adjusted OR = 1.29, 95% CI: 1.18-1.41,  $I^2 = 69.8\%$ ). However, use of H<sub>2</sub>RAs was not associated with an increased fracture risk (adjusted OR = 1.10, 95% CI: 0.99-1.23,  $I^2 = 86.3\%$ ).

### Subgroup meta-analyses

A positive association between the use of PPIs and fracture risk was observed in all types, but a positive association between the use of H<sub>2</sub>RAs and fracture risk was found only when nested case-control studies were combined (adjusted OR = 1.20, 95% CI: 1.13-1.28,  $I^2 = 0.0\%$ ) or when cohort studies were combined (adjusted OR = 1.08, 95% CI: 1.02-1.13,  $I^2 = 0.0\%$ ). In contrast, no significant association was observed in case-control studies (adjusted OR = 1.11, 95% CI: 0.81-1.51,  $I^2 = 85.6\%$ ).

Grouping of studies according to methodological quality showed a significantly increased fracture risk with PPI use in both high-quality studies (adjusted OR = 1.32, 95% CI: 1.18- 1.47,  $I^2 = 63.7\%$ ) and low-quality studies (adjusted OR = 1.25, 95% CI 1.06- 1.48,  $I^2 = 78.7\%$ ). There was also a significant positive association between H<sub>2</sub>RA use and fracture risk in high-quality studies (adjusted OR = 1.13, 95% CI: 1.05-1.21,  $I^2 = 40.3\%$ ) but not in low-quality ones (adjusted = OR 1.09, 95% CI: 0.87-1.38,  $I^2 = 90.6\%$ ).

Grouping studies by the number of patients showed marginally no association between PPI use and fracture risk (adjusted OR = 1.16, 95% CI: 0.98-1.38,  $I^2 = 66.5\%$ ), but no significant association between H<sub>2</sub>RA use and fracture risk (adjusted OR = 1.11, 95% CI: 0.81- 1.51,  $I^2 = 85.6\%$ ).

When studies were grouped by fracture outcome, the authors found a significant positive association between PPI use and hip fracture risk (adjusted OR = 1.31, 95% CI: 1.11-1.54,  $I^2 = 88.4\%$ ) and vertebral fracture risk (adjusted OR = 1.56, 95% CI: 1.31-1.85,  $I^2 = 6.3\%$ ), whereas there was no significant association between PPI use and the risk of other fractures, or between H<sub>2</sub>RA use and risk hip or any other fracture.

In subgroup meta-analyses by duration of use, long-term use of PPIs increased the risk of any fracture (adjusted OR = 1.30, 95% CI: 1.15-1.48) and the risk of hip fracture (adjusted OR = 1.34, 95% CI: 1.09- 1.66). There was no association between long-term use of H<sub>2</sub>RAs and either of these outcomes.

Grouping studies by dose, a significantly increased risk of hip fracture was observed for both high-dose use of PPIs (adjusted OR = 1.53, 95% CI: 1.18-1.97) and usual-dose use of PPIs (adjusted OR = 1.42, 95% CI: 1.31-1.53). In contrast, there was no association with hip fracture for either high-dose or usual-dose use of H<sub>2</sub>RAs.

Subgroup analyses by sex showed no significant association between PPI or H<sub>2</sub>RA use and hip fracture risk in men, or with hip fracture or vertebral fracture risk in women.

### Discussion

In this meta-analysis of observational studies, the authors found that the use of PPIs was associated with a moderate increase in the risk of fracture compared with nonuse of PPIs, whereas no significant association was observed between H<sub>2</sub>RA use and this risk. Similarly, long-term PPI

use and any dose of PPIs increased the risk of fracture in a meta-analysis of all the studies reporting duration of use and dose, whereas for H<sub>2</sub>RAs neither long-term use and nor use of any dose was significantly associated with fracture risk.

No significant association was found between use of H<sub>2</sub>RAs, which are less potent acid inhibitors than PPIs, and fracture risk. On average, H<sub>2</sub>RAs block only 70% of gastric acid production, whereas PPIs suppress acid production by up to 98%<sup>[68-70]</sup>. More prolonged exposure to H<sub>2</sub>RAs may be necessary to observe similar effects on fracture risk, although long-term use of these agents was not found to increase risk. These results suggest that H<sub>2</sub>RAs and PPIs may have differing effects on bone metabolism.

Some studies suggest that H<sub>2</sub>RAs may have antiresorptive properties<sup>[71,72]</sup> and even increase bone mineral density, which could decrease fracture risk<sup>[66]</sup>. Cimetidine also has been shown to prevent osteoclast differentiation induced by histamine<sup>[73,74]</sup>. Because of the possible mixed effects of H<sub>2</sub>RAs on bone health, data regarding long-term use of these drugs and fracture risk<sup>[63,64,66,67]</sup> or bone mineral density<sup>[75]</sup> have been inconsistent.

In contrast, PPIs have been shown to inhibit gastric proton pumps at physiological concentrations, whereas the inhibition of osteoclast and other tissue H<sup>+</sup>/K<sup>+</sup>-ATPase activity, such as osteoclast proton pumps, is much less pronounced<sup>[76]</sup>. It was, however, noted that the use of H<sub>2</sub>RAs was associated with a mild increase in fracture risk in studies having high-quality methodology (NOS score > 7) and in studies adjusting for at least 5 variables, but not in studies having low-quality methodology and adjusting for fewer than 5 variables. Further research in this area is needed.

Interestingly, the subgroup meta-analyses by the number of adjustment variables showed a significantly increased risk of fracture for both PPI and H<sub>2</sub>RA use when the data were adjusted for at least 5 variables. The results for H<sub>2</sub>RAs conflict with those of Vestergaard *et al.*<sup>[66]</sup>, who reported a statistically significant protective effect with use of these drugs for any fracture and for hip fracture. The positive association they found between H<sub>2</sub>RA use and fracture risk in studies with a high level of statistical adjustment may also be consistent with the marginal association they observed in high-quality studies (NOS score > 7).

Several potential mechanisms by which PPI therapy may lead to fractures have been identified. Firstly, the small intestine's ability to absorb ingested calcium salts depends on pH<sup>[77,78]</sup>. Calcium solubility is believed to be important for its absorption<sup>[79]</sup>, and an acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts<sup>[80]</sup>. Secondly, impaired calcium absorption might lead to compensatory secondary hyperparathyroidism, which may increase the rate of osteoclastic bone resorption. Thirdly, PPIs may interfere with the resorptive activity of osteoclasts. Without osteoclast activity, old bone cannot be replaced,

predisposing patients to fractures<sup>[21,67]</sup>. However, further research is required to determine the precise effect of long-term use of PPIs on bone mineral metabolism<sup>[65]</sup>. Finally, gastric parietal cells appear to have a potent endocrine role in secreting estrogens<sup>[81,82]</sup>. Atrophy of the gastric mucosa, observed in patients infected with CagA-positive *Helicobacter pylori*<sup>[83]</sup>, reduces the number of gastric parietal cells and may decrease local production of estrogens. Estrogens produced in the stomach directly induce expression and production of ghrelin<sup>[84,85]</sup>, which appears to increase bone formation by osteoblasts<sup>[86]</sup>.

## CONCLUSION

Clinicians should carefully consider any decision to prescribe ASDs, especially for patients who are already at risk for pneumonia<sup>[87]</sup> and fracture<sup>[88-90]</sup>. Since it is unnecessary to achieve an achlorhydric state in order to resolve symptoms, we recommend using only the minimum effective dose of the drug required to achieve desired therapeutic goals.

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