Hip fracture and proton pump inhibitor therapy: Position statement

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There has been recent media attention to the possibility that long-term proton pump inhibitor (PPI) prescribing may be linked to an increased risk of hip fracture according to data from the United Kingdom (UK) (1) and Canada (2). The Canadian Association of Gastroenterology has prepared the following position statement on the association between PPI therapy and hip fracture in light of this evidence. The present position statement is outlined in greater detail elsewhere (3).

Yang et al (1) reported a nested case-control study using the UK General Practice Research Database that selected patients older than 50 years of age with an incident hip fracture, and age and sex-matched controls. There were 13,556 hip fracture cases and 135,386 controls; PPI therapy for more than one year was associated with an increased risk of hip fracture (adjusted OR 1.44; 95% CI 1.30 to 1.59). Targownik et al (2) reported a further nested case-control study using the Manitoba Population Health Research Data Repository, in which 15,792 patients with osteoporosis-related fractures were compared with 47,289 controls. There was no overall association between PPI use and fracture until after five or more years of exposure, when the risk of osteoporotic fracture became significant (adjusted OR 1.62; 95% CI 1.02 to 2.58). Similarly, the risk of hip fracture became significant after seven years of PPI exposure (adjusted OR 4.55; 95% CI 1.68 to 12.29).

The clinical significance of this is uncertain because extrapolation of these figures (assuming 1.8 per 1000 patients develop a hip fracture [1]) suggests that 1263 patients need to be treated with a PPI for more than one year to develop one excess hip fracture, although the number needed to harm may be much lower after seven years according to the Canadian study.

These studies use reputable databases and are rigorously conducted and analyzed appropriately. The discussions in both of these articles suggest quite strongly that the association they have found is likely to be causal. Large databases provide a wonderful opportunity to evaluate benefits and harms of medical interventions, but caution must be exercised before assuming the latest finding represents a risk to patients. The ready availability of databases means that literally millions of associations can be tested; even within a particular hypothesis there are a variety of approaches to splitting the data (eg, duration of therapy, therapy dose, length of follow-up, patient age, male versus female). Researchers and journals are prone to emphasize positive findings and tend to underplay the role of chance or confounding factors. These issues are less likely to be important if a consistent association is found. An accompanying editorial (4) to the Canadian study also cites a third Danish database study (5) that supports an association between PPI therapy and fracture. It is interesting to note that the Danish study had a much greater number of cases (124,655) than the other two studies, and yet had much more muted conclusions and was published in a lower impact factor journal.

The Danish study was circumspect in their conclusions because there were inconsistencies in the data and there was no dose response information. For example, there seemed to be an increased risk with taking less than 25 doses of a PPI in one year with a lower (but still statistically significant) risk in those taking one dose per day for a year. There seemed to be no biologically plausible hypothesis why such infrequent use of PPI therapy would be associated with an increased risk of fracture. There were also inconsistencies with the UK and Canadian studies. The UK study reported an increased risk of hip fracture after one year of PPI therapy; there seemed to be little increase in risk over the next four years, whereas the Canadian study only found a significant association after seven years. Targownik et al (2) suggest that perhaps the UK database included patients that had in fact been taking PPIs for much longer; however, this is speculation.

Furthermore, a Canadian cohort study (6) followed-up on elderly patients in Ontario on warfarin (n=52,701), thyroid replacement (n=40,555), oral corticosteroid (n=43,915) and PPI therapy (n=60,383) for five years. There was no increased risk of hip fracture in those taking warfarin compared with those on PPI therapy (adjusted OR 0.94; 95% CI 0.81 to 1.09), but there was an increased risk with corticosteroid therapy compared with PPI therapy (adjusted OR 1.44; 95% CI 1.21 to 1.70). It could be that warfarin is also associated with an increased risk of hip fracture; however, it is interesting that Targownik et al (2) found little increase in fracture risk in those taking anticoagulants (14.5% of fracture cases taking anticoagulants compared with 13.4% of controls).

Finally, there is the issue of biological plausibility. It has been proposed that acid suppression may reduce calcium absorption and increase the risk of fracture (1). The role of pH in calcium absorption is, however, controversial. The dissolution of calcium carbonate is pH-dependent in vitro, although the clinical significance of this is uncertain given that calcium

is absorbed in the small intestine where the pH is nonacidic regardless of stomach pH. A review of the literature (7) identified seven randomized trials that evaluated calcium absorption with acid suppression in healthy subjects or those with ulcer disease. There were major methodological issues with many of the studies and they were all small. Four studies found no impact on calcium absorption while three reported decreased absorption. Further work is needed in this area, but there are no conclusive data that would make the association between fracture and PPI biologically plausible. Furthermore, some research suggests that PPI therapy may inhibit bone resorption (8), which may protect against fracture risk.

PPIs are one of the most well-tolerated classes of drugs on the market. They have also improved the quality of life of countless patients with acid-related disease. There are risks in prescribing any drug and this should be borne in mind by all prescribing clinicians. PPI therapy should only be prescribed for indications where there is a proven or likely benefit and the need for these drugs should be reviewed on a regular basis. This applies particularly to frail and elderly patients with multiple comorbidities and those taking a number of different medications where the possibility for drug interactions increases. This message applies to all the drugs clinicians prescribe including PPI therapy. Current data would not support particular care in prescribing PPI therapy due to concerns about the risk of hip fracture. There is no persuasive evidence that the association is causal, although this can never be excluded as a possibility. The Canadian Association of Gastroenterology encourages health professionals to keep continually updated on the medical literature and will endeavour to disseminate further guidance if more information on the possible harms of PPI therapy becomes available.

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