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Examining the Potential Relationship Between Proton Pump Inhibitor Use and the Risk of Bone Fracture

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G&H Proton pump inhibitors have generally been known for their overall efficacy, safety, and widespread use for treating gastroesophageal reflux disease. How was the possible link to an increased risk of bone fracture first discovered?

DCM Over the past decades, proton pump inhibitors (PPIs) have been shown to be the therapy of choice for gastroesophageal reflux disease due to their proven superiority over other medical therapies, such as H_2-receptor antagonists. PPIs have also shown superiority over H_2-receptor antagonists for the other 2 major indications for long-term acid suppression: hypersecretory states and prophylaxis for nonsteroidal anti-inflammatory drug (NSAID) gastropathy. However, PPIs should not necessarily be considered first-line therapy for other gastrointestinal complaints, and at times, PPIs are overprescribed for dyspepsia and other nonspecific foregut complaints.

The possibility that PPI use may be associated with an increase in the risk of bone fracture was first reported in 2006 by 2 independent groups. Vestergaard and associates showed a positive association between PPIs and bone fracture risk without a dose or duration effect, whereas the study conducted by my colleagues and I, which analyzed the United Kingdom General Practice Research Database, identified both a dose and duration effect. (All epidemiologic analyses are limited by the potential for confounding; if a dose and/or duration effect can be shown in an analysis, it lends credence to the validity of the association.) Before conducting our study, my colleagues and I had hypothesized that bone fracture would be less frequent in patients who were exposed to PPIs. However, as has been widely cited since our study was published (and in agreement with the study by Vestergaard and colleagues), our results showed the exact opposite. We subsequently performed another analysis in patients with a naturally occurring cause for hypochlorhydria (pernicious anemia) and found a similar relationship, suggesting that our finding was accurate and potentially directly mediated by acid suppression.

G&H How did you explain this unexpected relationship?

DCM After our study and many subsequent studies by other researchers, a working hypothesis to explain the relationship between PPI exposure and fractures has emerged. We believe that suppression of gastric acid secretion may impair effective calcium absorption and, therefore, predispose patients to possible fractures due to osteopenia. Our supplementary study mentioned above supports this hypothesis, and other studies in humans have demonstrated that gastric pH affects calcium absorption. However, epidemiologic (ie, population database) studies do not lend themselves to interventions in which only some PPI patients receive calcium replacements in a double-blind, randomized fashion; thus, it is not possible for these types of studies to definitively prove the hypothesis. In addition, the available epidemiologic databases do not provide information on dietary and/or over-the-counter supplements, so it is not possible to stratify results based on the calcium intake of these patients. Finally, surrogate marker trials, such as the epidemiologic bone density trial by Targownik and associates, have failed to identify reduced bone density in patients who were exposed to long-term PPI therapy compared to patients who were not exposed to PPIs. In short, it is still unknown whether the risk of bone fracture can be mitigated by providing excess oral calcium to improve calcium absorption.

G&H Can we conclude that PPI use increases the risk of bone fracture? What is the current understanding of this relationship?

DCM As originally suggested by our epidemiologic study—as well as by a number of other studies and, more recently, a large meta-analysis—it appears that there is a small increased likelihood of developing a bone fracture in a patient taking long-term PPIs. In addition, there is likely a dose response, such that the higher the dose (or the longer the duration of therapy), the more likely it will be that a patient will develop a bone fracture. Thus, the association appears to be small but real, and it is potentially relevant in elderly individuals, many of whom are already at risk for osteopenia and fractures, which have a major impact on quality of life and are drains on healthcare resources. Consequently, when considering acid-suppressive therapy, my usual approach is to first determine whether the patient truly has an indication for a PPI and, if so, to use the lowest effective maintenance dose, which depends on the indication.

G&H What are the main indications for long-term PPI use?

DCM There are 3 main indications for long-term PPI use. The first indication is reflux disease. In the absence of documented erosive disease or Barrett esophagus, I favor the use of on-demand PPI therapy. If reflux patients have Barrett esophagus, documented erosive esophagitis, or significant symptoms despite on-demand therapy, they should be placed on a once-daily dose of PPI therapy. I support the use of twice-daily PPIs only rarely in patients with reflux (eg, when patients have documented suboptimal control while on a once-daily PPI and have findings from an impedance pH test that support higher-dose therapy). The old adage "if once-daily therapy is good, then twice-daily therapy is better" probably does not hold true when it comes to long-term PPI use.

The second indication for long-term maintenance PPI therapy is nonsteroidal gastropathy. With all of this recent interest surrounding the potential risks of PPIs, there may be many patients who are not taking PPIs but should be. Nonsteroidal gastropathy is a significant disease. According to an old paper by Singh and colleagues, approximately 80% of 1,920 patients on NSAIDs who presented with life-threatening upper gastrointestinal bleeding did so without any preemptive symptoms, demonstrating that it is important to prevent risk rather than wait to treat symptoms when they develop, as the first symptom can be life-threatening. Studies have shown that the risks of nonsteroidal gastropathy increase with a history of prior peptic ulceration (bleeding or nonbleeding), concomitant therapy with anticoagulation, concomitant therapy with steroids, increasing age, and taking more than one NSAID simultaneously; if such patients are ever placed on NSAIDs, they should also be placed on a once-daily PPI. In these settings, a once-daily PPI reduces the likelihood of a life-threatening event by approximately 50%. Therefore, PPIs should be continued long term in these patients despite potential side effects, including a slightly increased risk of bone fracture.

The third indication for long-term maintenance PPI therapy is a hypersecretory state. Although this condition is rare, it can be life-threatening, and suppressing high levels of acid output can save the lives of these patients. In these patients specifically, I support the use of twice-daily PPI maintenance therapy, and I also try to titrate the PPI dose to acid output levels if possible.

G&H Despite the potential risk of bone fracture, do you support the use of PPIs in all patients with any of these indications?

DCM I believe that denying therapy to patients with these 3 indications exposes the patients to significant risk. Rather than focusing too much on the risks associated with PPIs, we should be balanced and use these drugs appropriately in the individuals who need them and avoid these drugs in individuals who do not need them. Clearly, there has been some PPI overuse in patients who do not have classic reflux disease or hypersecretory states or who do not use NSAIDs. In such patients who are taking PPIs, physicians should reevaluate whether the drugs are truly indicated and should consider slowly weaning these patients off of PPIs to prevent possible rebound gastric acid hypersecretion and to potentially limit long-term side effects.

G&H What is considered long-term PPI use, and are there any alternatives?

DCM Therapy lasting more than 8 weeks is usually considered to be long-term treatment, but in reality, we are talking about years of treatment. Most studies of reflux patients with documented healing of erosive esophagitis have followed patients for 6 months; a few maintenance trials that were used to obtain approval for long-term PPI therapy for gastroesophageal reflux disease went out to 3 years in order to specifically assess for adverse events. A clinical study by Klinkenberg-Knol followed patients for as long as 11 years. Long-term use signifies chronic use. Reflux disease cannot be cured by acid suppression, which merely treats the effects of acid. The underlying pathophysiology of reflux is not hypersecretion; rather, it is the translocation of appropriate amounts of acid from the stomach to the esophagus, which is an inhospitable location.

Therefore, it could be argued that instead of long-term PPI use, it might be appropriate to perform a surgical fundoplication in gastroesophageal reflux disease

patients to avoid the use of long-term PPIs and eliminate the associated risks. However, fundoplication itself potentially involves additional morbidity (at reasonably high levels even in the best hands) and mortality (albeit at very low levels), as well as the risk of breakdown and loss of efficacy over time. Many gastroenterologists have documented cases in which a patient underwent a fundoplication that was successful for many years, but the patient's symptoms eventually began to recur as the fundoplication broke down. Several cost analyses have examined the costs of fundoplication versus PPI maintenance. The crossover point appears to be approximately 10 years (ie, if the fundoplication lasts more than 10 years, it might be more cost-effective to operate on the patient). However, even with the most experienced surgeon, a fundoplication has potential risks and morbidity.

G&H Should all patients who are taking PPIs also take calcium supplementation or undergo screening for osteoporosis?

DCM In my opinion, any person who is potentially at risk for osteoporosis (eg, any elderly person or postmenopausal woman) should undergo bone-density studies and screening for osteoporosis, whether or not he or she is taking PPIs. I do not believe that special interventions—such as undergoing a dual-emission X-ray absorptiometry (DXA) scan at an earlier age—should necessarily be performed merely because of PPI use. However, the general guidelines for osteoporosis screening should be followed.

That being said, I recommend that individuals on long-term PPI therapy make sure that they have a good calcium intake (although I recommend that all patients have a good calcium intake, whether or not they are taking PPIs). No studies have compared PPI users taking calcium supplementation with PPI users who are not taking calcium supplementation; therefore, it is unclear whether calcium impacts a patient's outcome. Without any firm data to support the use of calcium supplementation, I do not think that it is incumbent on us to make any specific recommendations.

G&H Has the potential risk of increased fractures caused concern in patients taking PPIs?

DCM Absolutely. Unfortunately, when a prominent journal publishes a paper that disseminates information to the lay press, patients read the lay press articles and decide to take action on their own, such as unilaterally stopping PPI use because they are worried that they will develop fractures. After my study was published in 2006, many of my own patients came to my office, telling me that they had read in a newspaper that the drug I had prescribed for them was bad, so they had stopped using it, but now they were experiencing severe heartburn, and what was I going to do about it? Patients may be informed, but they do not necessarily take into account the whole picture. Doctors should have a balanced discussion with their patients regarding all of the risks and all of the benefits of any drug that they prescribe before the start of treatment.

G&H What studies should be conducted to better understand the association between PPIs and the risk of bone fracture?

DCM I would like to see further study on the mechanism of possible osteopenia in these patients. Interestingly, a large Canadian study that recently looked at DXA scans did not find an increased risk of fracture according to bone density measurements; this finding contradicts an earlier finding by the same group of researchers that showed an increased risk of fracture with PPIs. This recent finding raises the possibility of other mechanisms for fracture, such as parathyroid hormone dysfunction, or perhaps the finding shows that measurement of bone density is imprecise and other surrogates, such as clinical chemistry measures of bone turnover, should be employed instead.

To better understand the magnitude of the potential risk between bone fracture and PPI use, a double-blind, randomized study should be conducted to compare treatment with and without calcium supplementation and with and without PPI exposure. Although the risk of bone fracture may be increased with PPI use, its magnitude may be minor and may be overcome with appropriate calcium intake. To obtain an initial look into this issue, animal studies should be conducted, as this study cannot be performed easily in humans and should not be performed in rats because of their different physiology. A larger mammal would be necessary.

Suggested Reading

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