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EDITORIALS

Balancing the Risks and Benefits of Proton Pump Inhibitors

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Proton pump inhibitors (PPIs) are one of the most widely used classes of medications in the United States and worldwide. This is largely because they are extremely potent suppressors of gastric acid[1] and are therefore more effective than alternatives, such as histamine-2 receptor antagonists (H_2RAs) for common gastric acid-related problems, such as gastroesophageal reflux disease (GERD)[2] and peptic ulcer disease.[3,4] Because they are so effective, PPIs are recommended by national guidelines as first-line therapy for more serious problems related to gastric acid, such as erosive esophagitis and Barrett's esophagus.[2] They are also preferred as cotherapy with nonsteroidal anti-inflammatory drugs (NSAIDs) for patients who are at high risk of gastrointestinal complications, such as gastrointestinal bleeding.[5] Finally, PPIs are also preferred to H_2RAs for maintenance therapy in patients with gastric acid hypersecretory states.

As PPIs have become more widely used, concerns have emerged regarding their potential for adverse effects and long-term harm. One adverse effect that has received increasing attention is osteoporotic fractures. Several observational studies have shown an association between long-term PPI use and fractures of both the hip[6,7] and vertebrae.[7] This increased risk is thought to be due to achlorhydria, leading to malabsorption and deficiencies of calcium and vitamin B_{12} and subsequent bone loss.[8] There has been some uncertainty about this risk, however, because these

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studies are observational, and other studies have found no association between PPIs and osteoporosis or bone loss[9] and no association between PPIs and B_{12} deficiency in elderly patients.[10]

The article by Eom and colleagues in this issue of the *Annals* helps to clarify this issue.[11] They report the first meta-analysis of the association between PPIs and fracture risk. The meta-analysis included 5 case-control studies, 3 nested case-control studies, and 3 cohort studies. The authors concluded that PPIs are associated with a 29% increased risk of fracture, including 31% increased risk of hip fracture and a 54% increased risk of vertebral fracture. These findings were robust and were consistent across all types of studies, for both low- and high-quality studies, for both long-term use (defined as greater than 1 year) and any use, and for both usual doses and high doses. This increased risk was not consistently shown for H_2RAs. H_2RAs were associated with a small increased risk of fracture only for high-quality studies (odds ratio = 1.13; 95% confidence interval, 1.05-1.21), but this association was not significant across all types of fractures or all types of studies. Unfortunately, the meta-analysis was not able to include randomized controlled studies, because none have been reported. Even so, this study helps to guide practicing clinicians by summarizing the best available evidence, and the authors' findings are convincing in their conclusion that PPIs (but not H_2RAs) are associated with an increased risk of fracture.

It should be noted that in the absence of randomized control data of the effects of PPI exposure on bone metabolism and fractures, one must remain cognizant of the unexpected confounders that may affect the available epidemiological studies. One obvious potential confounder is confounding by indication, whereby sicker individuals receive the intervention (ie, PPI therapy), and the outcome (ie, fractures) is due to some other factor related to their underlying illness. In addition, it should also be pointed out that none of the studies in the meta-analysis had firm information about supplementary calcium intake for the individuals studied. It may be that simple calcium supplementation could negate the deleterious effect of PPIs on bone density. In fact, a recent General Practice Research Database study of fracture risk in patients with achlorhydria resulting from pernicious anemia (which is associated with gastric atrophy) also found an association similar to that of PPI use even after correcting for vitamin B_{12} replacement.[10]

Fractures are not the only potential adverse effects that clinicians should be concerned about when prescribing PPIs. Studies have shown PPIs to be associated with a twofold increase in the risk of *Clostridium difficile* colitis and a more than threefold increase in the risk of other enteric infections.[11] PPIs may also be associated with an increased risk of ambulatory pneumonia, although this association is subject to controversy.[8] There have been cases of PPI-induced acute interstitial nephritis, but controlled studies have not yet been done to clarify this association.[8] More recently, the Food and Drug Administration (FDA) has issued a warning that PPIs can cause hypomagnesemia, and that clinicians should use caution particularly in patients on digoxin,[14] but again this association has not been elucidated through controlled studies. On the positive side, the initial concern that PPIs may cause gastrointestinal cancers has not been substantiated.[8]

So how should primary care clinicians weigh the risks and benefits of PPIs when treating patients for acid-related conditions? As with any treatment, the key is the balance of absolute risks and benefits, which will differ among patients with different conditions. For patients with potentially serious conditions, the balance is likely to fall on the side of treatment with PPIs. For example, clinicians should not be concerned about the risks of PPIs when treating patients with acute gastric or duodenal ulcers, especially because the initial concern is to heal the ulcer and avoid potentially life-threatening complications. The same would be true for long-term use of PPIs, when the PPI is used to prevent a potentially serious condition. Such examples would include using a PPI for gastroprotection in patients taking NSAIDs who are at high risk for gastrointestinal complications. National guidelines recommend cotherapy with PPIs for NSAID prophylaxis, not only when these patients have a history of peptic ulcers, but also in elderly patients or those taking warfarin, aspirin, or glucocorticoids.[5] In these cases, it would probably not be prudent for clinicians to withhold PPIs because of the risk of fractures. In fact, studies have found that clinicians underuse PPIs for these patients,[15] even when prompted that the patient is at higher risk for gastrointestinal complications.[16] PPIs are also appropriate for long-term maintenance in patients with established GERD and Barrett's esophagus or persistent symptoms (but only at standard doses approved by the FDA or for maintenance in patients with documented hypersecretory states).

The balance of risks and benefits would be quite different in patients who are being treated primarily for symptoms with little risk of serious complications. An example would be patients with nonspecific dyspepsia without alarm symptoms or predominant GERD symptoms and without evidence of *Helicobacter pylori* infection. Current US guidelines recommend empiric treatment with PPIs, but only for 4 to 6 weeks,[17] after which PPIs should be withdrawn or stepped down to less-potent therapy. Guidelines from other countries

recommend H_2RAs or antacids as initial therapy, with PPIs reserved for refractory cases, as this approach has been shown to be equally effective and less costly.[18] Using PPIs for long-term maintenance in these cases is usually not appropriate and probably represents the most common reason for overuse of PPIs.

Another area where PPI use can be reduced is in maintenance therapy for GERD. Because PPIs are extremely effective for GERD, it would not be clinically appropriate to avoid their use as initial therapy or as a therapeutic trial in patients with atypical symptoms, such as chronic hoarseness.[19] Regarding continuation or maintenance therapy, a good rule of thumb is to use the lowest effective maintenance dose for long-term control.[8] We believe that patients with documented erosive esophagitis or Barrett's esophagus should be maintained on once-daily PPI therapy, but those with uncomplicated GERD (ie, no erosive disease and no Barrett's esophagus) may be well served by on-demand PPI therapy[20] to maintain symptom control while limiting the risks for side effects.

The article by Eom and colleagues in the current issue of the *Annals* further reinforces the need for balancing risks and benefits for any therapy that one prescribes. PPIs have clear benefits in patients that require them, and they should not be denied to patients who are likely to benefit from them. On the other hand, long-term PPI exposure may lead to other unwanted effects and should be reserved for patients likely to benefit from them. They should not be used long-term for undifferentiated dyspepsia, but neither should they be denied for patients with established persistent GERD, NSAID risk, and hypersecretory states, while aiming for the lowest effective maintenance dose.

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