

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

The Advantages and Adverse Events Associated With Long-Term Use of Proton Pump Inhibitors



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G&H What are the most common indications for the long-term use of proton pump inhibitors?

PK The major indication for the long-term use of proton pump inhibitors (PPIs) is for the acute and long-term management of gastroesophageal reflux disease. PPIs are also used as prophylaxis against nonsteroidal anti-inflammatory drug injury or against gastrointestinal bleeding in patients who are on dual-antiplatelet or dual-anticoagulant therapy, as well as for the treatment of peptic ulcer disease, *Helicobacter pylori* infection, and eosinophilic esophagitis.

G&H What have studies shown regarding the safety and efficacy of continuous maintenance with a PPI?

PK PPIs have demonstrated an excellent safety profile over the last 30 years. In short-term studies, few, if any, side effects have been documented to be greater than with a placebo. Most short-term side effects, such as headache, nausea, and diarrhea, are relatively minor. Recently, several studies have suggested associations with various adverse events. However, the majority of physicians maintain a positive perception of the safety of PPIs based on the methodology of the studies and lack of side effects that have been observed directly.

Studies and clinical experience have demonstrated that PPIs are extremely effective. They maintain symptomatic remission, improve the quality of life for patients with acid-related diseases and PPI-responsive eosinophilic esophagitis, and decrease the risk of complications in patients taking nonsteroidal anti-inflammatory drugs and

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dual-antiplatelet therapy. The role of PPIs in preventing the progression of Barrett esophagus and esophageal cancer is debated, but they continue to be used in this setting.

G&H What potential adverse events are associated with long-term PPI therapy?

PK Quite a few adverse events have recently been associated with the long-term use of PPIs. Those that

have received the most attention are associations with bone fractures, gastrointestinal infections, dementia, cardiac-related events, and kidney disease. The US Food and Drug Administration has released warnings regarding hypomagnesemia, interactions with clopidogrel, osteoporotic-related fractures, and gastrointestinal infections. Adverse events that have been reported to a lesser extent include associations with some liver issues as well as muscle conditions such as rhabdomyolysis. Studies have also suggested that patients taking PPIs have an increased risk of gastric cancer and esophageal cancer.

G&H What is the strength of evidence to support these associations, and what is the likelihood of these associations being causal?

PK The balance of the evidence comes from case-control or retrospective studies using very large databases, meta-analyses, and a few observational studies. In most of these studies, the increase in relative risk is statistically significant; however, in general, the absolute risk is actually very small, if the data are even correct. There are many methodologic challenges with these studies, not the least of which are issues related to confounding. It is likely that PPIs are responsible for the genesis of fundic gland polyps and perhaps hypomagnesemia, although the mechanism of the latter is difficult to demonstrate. Although each of the published side effects or adverse events has a theoretical biologic plausibility, there has been little documentation that there is a direct cause and effect for any of the associated adverse events. Therefore, at this point, the likelihood of these associations being causal is subject to strong questions. We cannot ignore the data, but more research is clearly needed.

G&H What do current guidelines recommend regarding the use of long-term PPIs?

PK The official guidelines recommend using the lowest effective dose of PPIs needed to maintain symptom relief or to treat underlying conditions. Physicians should prescribe PPIs for indications and clinical situations in which they have shown clear benefit. If PPIs are not needed, they should be discontinued. Recent position statements and articles addressing the potential adverse events have reinforced these recommendations and have spoken directly of overuse and inappropriate use.

G&H Are certain patient populations more vulnerable than others to the adverse events or side effects of continuous PPI use?

PK Patients who are immunosuppressed and travelers who are at risk for gastrointestinal infections, particularly *Clostridium difficile*, are vulnerable to adverse events and should be watched carefully. Smokers with osteoporosis may be at increased risk for bone fractures associated with long-term PPI use. The elderly population tends to be vulnerable to adverse events of many medications, so long-term PPIs should be considered carefully. Patients with or at risk of developing renal disease should be approached with caution, as the origin of this association is still unclear. There are very few, if any, patients who should not use a PPI if one is needed, although alternative treatment options may be available.

G&H What alternative treatment options are available for patients who choose not to use PPIs long term?

PK Patients with gastroesophageal reflux disease have several treatment options from which to choose, including traditional antireflux surgery and its endoscopic alternative. Additionally, clinical trials of new procedures are underway. Patients can take H₂-receptor antagonists, although it is important that they understand the difference in efficacy of those drugs vs PPIs. Lifestyle and dietary interventions such as weight loss and varying the time of day that patients eat may be useful. However, these alternative treatments are all individual decisions; there is no absolute alternative that fits specific groups of patients.

G&H Have the potential safety risks that are associated with long-term PPI use affected patient perception of this form of therapy?

PK The potential safety risk of PPI therapy is a major topic right now, and certainly in my office, there has been a substantial number of patients who schedule appointments specifically to discuss long-term PPI use. Patients typically bring up issues that they have heard and read about or have been told about, ask to stop use of PPIs, or ask not to use them long term.

G&H What are the main points of discussion that gastroenterologists should cover with their patients regarding PPIs?

PK Gastroenterologists and patients should talk specifically about the reason these drugs are potentially needed, speak as objectively and as carefully as possible about the perceived adverse events and the issues related to substantiating their veracity, and carefully discuss the alternative treatment options in the context of risk vs

benefit of long-term PPIs compared with other forms of intervention.

G&H What are the priorities of research in this field?

PK Patients and physicians would benefit from well-designed studies that investigate intermediate markers of some of the disease endpoints, as has been done with dementia and bone disease. In particular, it would be advantageous to understand how PPIs affect the microbiome and whether changes influence some of the adverse events. Furthermore, assessing causality in the relatively short term and developing alternatives to PPIs that offer the same upside would be helpful. Another priority is conducting research to understand what happens to patients now and in the future when physicians attempt to stop the use of PPIs.

At this point, discussion of long-term use of PPIs is highly controversial. A drug class that has been a major benefit to patients has come under fire, perhaps for good reason. However, it is crucial that we look carefully at the genesis of the data and at the magnitude of the risks that are being suggested, and put them in context while we continue to conduct research to determine which, if any, of these adverse events are an actual concern.

Dr Katz has no relevant conflicts of interest to disclose.

Suggested Reading

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