ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Issues Related to BID Dosing of PPIs

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G&H Is single-dose proton pump inhibitor use effective in all patients with gastroesophageal reflux disease?

JI There is a general sense that gastroesophageal reflux disease (GERD) is a nonissue and that all patients do well on a proton pump inhibitor (PPI). More recent evidence reveals that almost 40% of patients who are prescribed a single-dose PPI for GERD continue to experience symptoms and that half of these patients take over-the-counter medication to supplement their PPI therapy for symptom control. I advise providers to ask their patients about their GERD symptoms because, while the vast majority in fact improve with therapy, a substantial proportion are not symptom-free and could benefit from additional intervention.

G&H Is there ever a real indication for twice-daily dosing of PPIs for GERD, or is twice-daily dosing always excessive?

JI There are certain patient populations for whom twice-daily (BID) dosing of PPIs is beneficial. Vaezi and colleagues at the Cleveland Clinic examined 250 patients who underwent esophageal pH monitoring for typical and extraesophageal symptoms of GERD. Thirty-one percent of patients with typical GERD symptoms and 30% of those with extraesophageal symptoms of GERD experienced abnormal pH monitoring when treated with single-dose PPIs. In comparison, 7% of those with typical GERD and 1% of those with extraesophageal GERD symptoms experienced abnormal pH monitoring when on BID therapy. Thus, in selected patients, BID therapy will normalize esophageal acid exposure in a greater proportion of patients compared to those who are treated with single-dose PPI therapy.

At the same time, excessive use of BID dosing is a common problem. My colleagues and I conducted a study to determine whether patients with typical GERD symptoms (heartburn or acid regurgitation) who were asymptomatic to BID PPI therapy could be stepped down to single-dose PPIs. Of 117 consecutive patients on BID PPIs who were stepped down to single-dose PPIs, 93 (79.5%) remained asymptomatic for at least 6 months after step down. The single factor that predicted failure of step down was prolonged duration of PPI use—for every year of additional PPI use, patients were 34% more likely to experience recurrent GERD symptoms during step-down management.

G&H What is the cost of PPIs to our healthcare system?

JI PPIs are a substantial cost. Even in this era of generic PPI availability, this is a multibillion dollar business in the United States. Although I remain convinced that the majority of PPI use is appropriate, my colleagues and I, as well as other researchers, have reported that overuse of PPIs contributes substantially to healthcare costs. In the small cohort discussed above that my associates and I examined, the costs of excessive PPI dosing was estimated to be $50,000.

We have also examined PPI overuse for indications outside of GERD. For example, the practice of administering PPIs for stress ulcer prophylaxis for patients in whom prophylaxis is not indicated was found to be excessive (22% of all non–intensive care unit admissions). However, even more distressing was the fact that the majority of patients who were erroneously prescribed prophylaxis were also discharged on PPIs, with total medication costs estimated to exceed $100,000 annually from one academic medical center.

G&H What are the side effects of long-term PPI use, particularly with BID dosing?

JI It is difficult to clearly determine what side effects result directly from PPI use because the total number of patients on PPIs is unknown. Moreover, as BID PPIs are not a US Food and Drug Administration–indicated dosage for GERD, it is challenging to document the adverse events associated with BID PPI dosing. Nevertheless, there are potential side effects of PPIs, including osteoporosis leading to hip fracture, community-acquired pneumonia, *Clostridium difficile* infection, vitamin B12 deficiency, and hypomagnesemic hypoparathyroidism.

Additionally, medication interactions have been postulated. The most widely discussed concern is the potential competitive inhibition of conversion of the prodrug clopidogrel to its active form via cytochrome P4502C19, which is also necessary for PPI metabolism. Although retrospective studies have conflicting conclusions regarding the potential clinical outcomes of myocardial infarction or the need for cardiac revascularization among patients treated with PPIs concomitantly with clopidogrel, the only randomized clinical trial comparing PPI versus placebo among patients at high risk of coronary events failed to demonstrate any increase in cardiovascular events among those taking PPIs with clopidogrel. Suffice it to say that the final word regarding PPI:clopidogrel interaction has not been written.

G&H Do all patients with GERD require lifetime PPI therapy?

JI Certainly, there are substantial numbers of patients with GERD who will require life-long therapy to control their symptoms. However, I never tell a patient that they require a specific drug or class of drugs for the remainder of their lives because therapy for most diseases evolves over time and it is unlikely that a patient will truly take one drug for the rest of their lives.

In a corollary study to the PPI step-down study described above, my associates and I conducted a trial in which patients with GERD symptoms rendered asymptomatic on single-dose PPIs were stepped-off this therapy to either histamine receptor antagonists or no GERD therapy. Forty-one of 71 (58%) patients in whom PPIs were discontinued remained without GERD symptoms after 1 year of follow-up. Younger age and a dominant symptom of heartburn (as opposed to acid regurgitation) were predictors of failure of step-off therapy. This lends additional support to the view that not all patients in whom PPIs were necessary to alleviate symptoms require life-long PPI therapy to maintain symptom control.

G&H Are there any other common challenges when treating these patients?

JI Primary-care providers often fail to understand the difference between heartburn and dyspepsia. The definition of heartburn, and therefore of GERD, is a burning sensation originating behind the breastbone and radiating cephalad. Conversely, dyspepsia consists of epigastric discomfort, pain, bloating, or early satiety, and excludes the symptom of heartburn. I believe that this is one of the principal reasons that many patients referred to my care with heartburn have been checked for the presence of *Helicobacter pylori* infection and have even been treated to eradicate the bacteria, despite no evidence to illustrate a benefit in reducing GERD symptoms.

Suggested Reading

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