

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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## The Current Use of Proton-Pump Inhibitor Therapy in Clinical GI Practice

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**G&H** In the setting of patients with gastroesophageal reflux symptoms, but no evidence of erosive esophagitis, are there any significant clinical differences among the currently marketed proton-pump inhibitor molecules?

**PK** In the scenario of a patient with heartburn, who is presumed to have gastroesophageal reflux disease (GERD), but in whom there is no evidence of severe erosive esophagitis, each of the proton-pump inhibitors would be clinically indistinguishable if given at the US Food and Drug Administration–approved dosage.

There are head-to-head studies, principally in patients with erosive esophagitis, that on some occasions have shown a slight advantage in terms of symptom control for a given agent. In the very large studies of esomeprazole (Nexium, AstraZeneca), the symptom advantage for esomeprazole therapy over therapy with lansoprazole (Prevacid, TAP) is statistically significant, but for all practical purposes, clinically unimportant. In several other studies, lansoprazole has been shown to provide slightly improved and slightly more rapid symptom relief than omeprazole.

Although it is hard to imagine a scenario where these differences would be significant in the treatment of a large population of patients, it is important to note that each individual patient may react differently to differ-

ent therapies, and may have considerably more favorable results taking a specific proton-pump inhibitor. Furthermore, despite the similarity among proton-pump inhibitors in the overall management of GERD, there may be a small advantage for esomeprazole as the most efficacious therapy in the setting of severe erosive esophagitis.

**G&H** Are generic proton-pump inhibitors less expensive and as effective as the branded formulations?

**PK** The only currently available generic proton-pump inhibitor is omeprazole. Because there are no direct studies of generic omeprazole against branded omeprazole (Prilosec, AstraZeneca), one can only presume that if the manufacture of the molecule is the same, it should be of similar clinical effectiveness when compared to the nongeneric.

It is difficult to know whether the generic proton-pump inhibitors will ultimately prove to be the least expensive formulations, as this depends on several factors including marketing decisions, formulary bidding, and other related concerns. On the retail market, costs of generics sometimes depend on the geographic area where they are being purchased. Overall, the consistently least expensive proton-pump inhibitor for patients paying cash is most likely over-the-counter omeprazole (OTC Prilosec).

**G&H** Has the availability of an OTC proton-pump inhibitor formulation changed patient behavior in terms of seeking care from a gastroenterologic specialist? Are more serious gastroenterologic conditions going undiagnosed due to patient self-care?

**PK** The labeling for OTC omeprazole allows for 14 days of continuous use, with repeated courses every 4 months. Before taking longer courses or courses at shorter intervals, patients are advised to seek the care of a physician. Therefore, in principle, the need for continuous or long-term use of the OTC product should encourage patients to seek the care of a physician. In the literature, there is little evidence that empiric use of proton-pump inhibitors will truly hide the symptoms of a malignancy.

Patients with Barrett esophagus and Barrett-related cancers, because of the variable symptoms associated with these conditions, are often discovered on screening examinations, regardless of patients' care-seeking habits. Therefore, I do not believe that the use of OTC proton-pump inhibitors is preventing the diagnosis of more severe esophageal conditions. I can think of no anecdotal evidence of this from my own practice and I do not believe that there are data to show that OTC therapy has been detrimental in getting patients to physicians.

**G&H** What is the role of the immediate-release omeprazole formulation in the treatment of patients with GERD?

**PK** The immediate-release (IR) omeprazole product (Zegerid, Santarus) is unique in that the combination of bicarbonate and non-enteric-coated omeprazole granules offers, in theory, a more rapid onset of pH control. We have recently completed a study giving the IR omeprazole drug at bedtime, in comparison to two other proton-pump inhibitors, esomeprazole and lansoprazole, also given at bedtime for control of intragastric pH. IR omeprazole controlled pH more quickly compared to the other proton-pump inhibitors, which was not surprising, given that the other drugs are formulated to be taken before a meal. Conceptually, IR omeprazole offers the opportunity for on-demand use, particularly at bedtime in lieu of an H<sub>2</sub> receptor antagonist (H<sub>2</sub>RA), when nocturnal coverage is needed.

In my practice, which is strictly by referral, I prescribe IR omeprazole as a substitute for H<sub>2</sub>RA therapy at bedtime but not as an on-demand drug. I have used it as a daily-use drug in the patient who has breakthrough reflux symptoms and documented esophageal reflux during the overnight period. In a more typical GERD patient population, the added potential for IR omeprazole is as on-demand therapy especially at bedtime, for patients with predictable, intermittent nighttime symptoms. However, IR omeprazole is more expensive than an H<sub>2</sub>RA and should most likely be compared to H<sub>2</sub>RA therapy in the setting of intermittent use, in a controlled clinical trial.

**G&H** Has the availability of IR omeprazole encouraged the use of intermittent or on-demand therapy as a valid therapeutic approach?

**PK** If a patient is concerned with immediate symptom relief, the intellectual rationale for proton-pump inhibitor therapy, exclusive of IR omeprazole, is not strong. Unlike H<sub>2</sub>RAs and antacids, they are not formulated to work in this manner. However, for intermittent use in which patients need relief over a 1–3 day period, proton-pump inhibitors do seem to work. Though there have been very few studies that have looked at proton-pump inhibitors administered in this way and there is no on-label indication for this type of use, patients nevertheless take them on-demand. However, if a patient complains of heartburn and asks what he or she can do for immediate relief, we advise taking an H<sub>2</sub>RA or antacid, as these agents should provide more rapid relief than a single dose of a proton-pump inhibitor. If patients are on IR omeprazole, using this on-demand might work, but there are no studies to document this.

**G&H** Are any new agents or formulations currently being studied for GERD therapy?

**PK** There are several drugs in clinical trials that profess to be longer acting. Some of them are traditional proton-pump inhibitors that, through a longer delay of release or an increased half-life of the molecule, control pH levels for a longer period. A novel drug class that has been examined, the acid pump antagonists (P-CABs) that inhibit potassium channels, may no longer be under investigation

due to the difficulty in showing improvement in clinical efficacy when compared to esomeprazole.

**G&H** What other issues are of concern when considering the administration of proton-pump inhibitor therapy?

**PK** One of the key issues in administering proton-pump inhibitors, regardless of the choice of agent, is optimization of pH control through careful dose timing. In the clinical arena, proton-pump inhibitors seem to achieve efficacy when given before a meal, probably 30–60 minutes though the exact time is not known. In the case of a patient needing high-dose proton-pump-inhibitor therapy, before breakfast and before dinner are the optimal dosing periods, with the caveat that the IR omeprazole

molecule potentially can be used at bedtime, though more data are needed regarding the clinical efficacy of this practice.

**Suggested Reading**

Katz PO. Review article: putting immediate-release proton-pump inhibitors into clinical practice—improving nocturnal acid control and avoiding the possible complications of excessive acid exposure. *Aliment Pharmacol Ther.* 2005;22 (suppl 3):31-38.

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Miner P Jr, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol.* 2003;98:2616-2620.

Katz PO, Tutuian R. Histamine receptor antagonists, proton pump inhibitors and their combination in the treatment of gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol.* 2001;15:371-384.



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