DEMEESTER FESTSCHRIFT

Proton Pump Inhibitors in the Management of GERD

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Abstract
Introduction Management of gastroesophageal reflux disease (GERD) is based on the concept that gastric contents, principally acid and pepsin, are responsible for symptoms of reflux and esophageal injury. Pharmacologic treatment is based on the principle that controlling intragastric pH will affect esophageal healing and subsequently symptom relief.
Results and Discussion Control of pH can be accomplished with antisecretory agents, principally proton pump inhibitors (PPIs). The majority of patients respond to a single daily dose of a PPI; however, some will require higher doses, and a small percentage are "refractory" to twice daily dosing of these drugs. The success of these agents, and in fact the reasons for "failure," is elucidated by understanding the mechanism of action of PPIs and the effect of dose timing and meals on their efficacy.
Conclusion Awareness of new concerns regarding potential side effects of PPIs when used long-term require careful thought as GERD is a chronic disease with most needing some form of medical treatment over time. This article reviews the pharmacologic properties of PPIs and the impact on the treatment of GERD.

Introduction

It is estimated that 30–40% of the US population have some symptoms of gastroesophageal reflux disease (GERD).[1] The most common symptoms are heartburn and/or regurgitation with an unknown number of patients with extra-esophageal symptoms, such as cough, laryngitis, or wheezing.[2,3] Chronic, frequent heartburn is the major risk factor for the development of esophageal adenocarcinoma, the fastest rising cancer in white men in the USA.

GERD is caused by the retrograde movement of gastric contents, mainly acid and pepsin, into the esophagus thereby causing symptoms of reflux and injury to the esophageal mucosa. Antisecretory agents, such as proton pump inhibitors (PPIs), increase intragastric pH thereby promoting esophageal mucosal healing and subsequent symptom relief. Understanding the mechanism of action of PPIs and the importance of dose timing in relation to meals is critical to optimize treatment for GERD. A majority of patients respond to a single daily dose of PPI. However, there are those who will require higher doses of medication and a small percentage that are considered refractory to PPIs. PPIs are safe medications with a low side effect profile; however, there is a new concern regarding the potential for long-term effects of these medications in the treatment of a chronic GERD sufferers. This article will explain the pharmacology of PPIs and their impact on the treatment of GERD.

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Acid Production

The parietal cell is the key player of acid secretion in the stomach responsible for an average of 2 L of gastric acid daily.[4] It expresses receptors for stimulators of acid secretion, including gastrin released from G cells, acetylcholine released from the vagus nerve, and histamine. Gastrin and acetylcholine cause the release of histamine from enterochromaffin-like cells (ECL). Activation of gastrin and acetylcholine receptors results in the activation of the protein kinase C phosphoinositide signaling pathway. Histamine leads to activation of adenylate cyclase and increase in cyclic AMP.[5,6] Both of these signaling pathways regulate a series of kinase cascades that control the acid secreting, H+/K+ATPase (proton pump), the target of the PPI.

PPIs inhibit only active pumps. A single dose of a PPI does not inhibit all pumps and does not result in profound inhibition of acid secretion. Acid production is inhibited with subsequent PPI doses, taking 5–7 days to achieve a steady state. Acid inhibition is never complete because of continued synthesis of new proton pumps. When PPIs are given twice daily, more active proton pumps are exposed to drug, and steady-state inhibition of gastric acid secretion is achieved more rapidly and more complete.[7]

PPIs are weak bases, incompletely absorbed, and have short half lives (0.6–1.9 h).

PPIs accumulate and activate in the acid environment at the secretory canalicular surface of the parietal cell. The inactive benzimidazole is converted to a cationic tetracyclic sulfonamide, which bind to the alpha subunit of the H+ K+
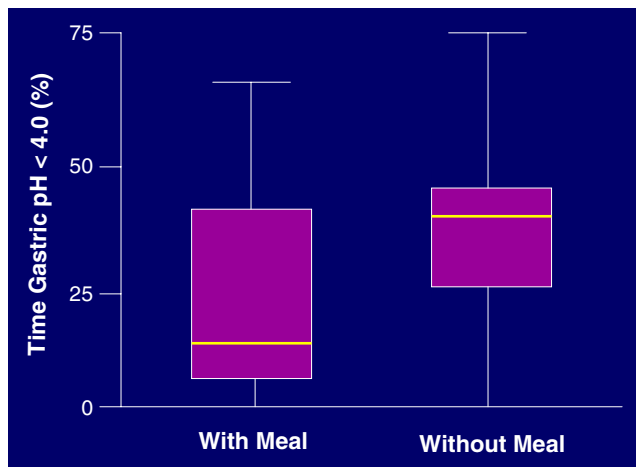
Table 1 Relationship Between Percent Time pH >4.0 and Healing of Erosive Esophagitis

Healing status	Mean % time intragastric pH>4.0[a]	P value
Healed	61.3	0.0002
Not healed	42.2	

Consistent with ITT analysis: 64.5% vs. 47.6% ($p=0.0003$). Overall erosive esophagitis was healed in 69.9% of patients at 4 weeks

ITT intention to treat

[a] Mean number of hours with valuable data was 23.64 h

ATPase enzyme, irreversibly inhibiting acid production in about 70% of active pumps.[5,8] Acid secretion returns when new H+ K+ ATPase molecules are converted from inactive status in the tubulovesicle to active form at the canalicular surface.[9] This averages 36–72 h. PPIs decrease daytime, nocturnal, and meal-stimulated acid secretion.[10] The slower a PPI is cleared from the plasma; the more of it is available to be delivered to the proton pump.[11]

All available PPIs are indicated for once daily dosing, usually in the morning. Food affects the bioavailability of each molecule, so it is our practice to recommend that all PPIs be given prior to meals for optimal efficacy. This is based on the concepts outlined above and results of intragastric pH studies in which superior daytime pH control (time intragastric pH>4) was seen when the PPI was taken before breakfast compared to an empty stomach (Fig. 1).[11]

PPIs are responsible for inhibiting gastric acid secretion, thereby decreasing potential damage to the esophageal mucosa. In addition, by raising gastric pH, the conversion of pepsinogen to pepsin, another player of mucosal damage, is inhibited. As one would expect, greater duration of gastric acid suppression affords greater healing rates of erosive esophagitis (Table 1).

Most patients respond to once-a-day PPI. However, some patients, particularly those with extraesophageal symptoms or complicated disease need higher doses. Splitting the dose and giving a PPI twice daily, before breakfast and dinner, results in superior nocturnal intragastric pH control, when compared to a double dose given once daily (Fig. 2).

Figure 1 Percentage time for which gastric pH <4 when taking PPI (either omeprazole 20 mg or lansoprazole 30 mg) each morning, either 15 min before a breakfast meal or without food and drink (except for water), until 12 noon. In this box-and-whiskers plot, the median values are indicated as the *transverse line within the box*, the interquartile range as the *vertical extent of the box*, and total range as the *whiskers*. Acid suppression was significantly more effective when medication was taken with breakfast than without ($p<0.01$).

Pharmacodynamic Effects

Omeprazole (also available over the counter at a 20 mg dose), lansoprazole, pantoprazole, rabeprazole, esomeprazole, and the newest PPI omeprazole sodium bicarbonate immediate release (IR-OME, Zegerid®) are all available for the treatment of GERD. PPIs inhibit daytime, nocturnal, and meal-stimulated acid secretion to a significantly greater

Figure 2 Bar graph showing percent time nocturnal pH <4 (10P-6A) for three different dose regimens of omeprazole. All result in equal daytime pH control. Results are similar with all proton pump inhibitors.
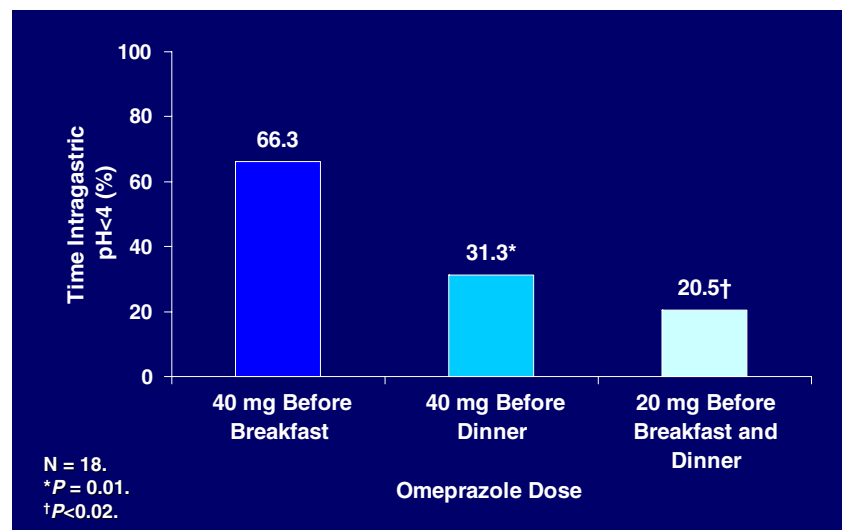
degree than H$_2$RAs and have largely replaced these agents in antireflux therapy.

Usually, delayed release PPIs are administered before the first meal of the day. If a second dose is needed, it should be given before the evening meal. With the exception of IR-OME, bedtime dosing is discouraged because proton pumps are not stimulated to a great degree during the sleeping period. When PPIs are administered twice daily, more active proton pumps are exposed to drug, and steady-state inhibition of gastric acid secretion is quicker and more complete. Daily dosing of PPIs are thus more effective than on demand or intermittent dosing in maintenance of symptom relief and healing of erosive esophagitis.

Patients with *Helicobacter pylori* gastritis involving the gastric corpus have enhanced overnight intragastric pH control with PPIs compared to those who are *H. pylori* negative.[12] However, *H. pylori* infection has little effect on pH control and thus has no role in the management of GERD. We do not routinely test for *H. pylori* in our GERD patients and find that it has no effect on outcome.

Immediate-Release Omeprazole

The newest PPI, immediate-release omeprazole sodium bicarbonate (IR-OME), offers another option for nighttime heartburn sufferers. IR-OME suspension, when administered at bedtime, achieved enhanced control of nocturnal gastric pH when compared to pantoprazole 40 mg.[13] Additionally, IR-OME given prior to breakfast and dinner, was found to be more effective in controlling overnight pH as compared to twice daily pantoprazole.[13]

An open-label, randomized, crossover study (*N*=54) compared intragastric pH with IR-OME suspension 40 mg, lansoprazole 30 mg, and esomeprazole 40 mg given at bedtime (10:00 P.M.) on an empty stomach for 7 days.[14]

In the first half of the nighttime, intragastric pH >4 were higher after IR-OME compared to esomeprazole or lansoprazole (*p*<0.001, both comparisons).[15] Acid control with IR-OME was significantly better than lansoprazole (*p*< 0.001) and comparable to esomeprazole for the entire nighttime period. The percentage of time with gastric pH >4 for the entire 24-h period was 43.6% after treatment with IR-OME vs. 59% with esomeprazole (*p*<0.001) and 27.8% with lansoprazole (*p*<0.001), when compared with both IR-OME and esomeprazole (Table 2).[14]

This study further supports the longstanding suggestion that delayed release PPIs are not optimally effective when given at bedtime. Lansoprazole offered a slow onset of overnight control with little increase the next day. Esomeprazole had a slower onset, with little time pH >4 in the first part of the sleeping period, however, had excellent 24-h control. As such, delayed release PPIs are best given before the evening meal if control is needed overnight.[16]

Side Effects of PPIs

PPIs have a low side effect profile and are considered to be safe medications. Frequent side effects seen in trials include headache, abdominal pain, and diarrhea. However, they are no greater in frequency than placebo.[15]

The increased levels of gastrin from gastric acid suppression and its trophic effects on stomach mucosa have also been a concern. Fundic gland polyps, while seen in a small number of patients, have not been shown to lead to a negative outcome. In the absence of observational and case–control studies, we do not change or stop PPIs due to fundic gland polyps unless the patient requests an alternative approach. We do not perform surveillance endoscopies unless a patient has a change in symptoms.

Table 2 Percent Time pH >4 Overnight with Bedtime Dosing of PPIS

Treatment	2200–2400 hours	First half of the night, 2200–0200 hours	2200–0400 hours	Entire nighttime period, 2200–0600 hours
IR-OME 40 mg	32.3 (6.6–94.1)	51.9 (16.8–88.7)	62.6 (26.0–88.1)	53.4 (31.3–90.3)
Lansoprazole 30 mg	0.0 (0.0–0.3)[a]	12.0 (0.0–32.1)[a]	26.6 (2.8–43.9)[a]	34.2 (13.3–52.2)[a]
Esomeprazole 40 mg	0.1 (0.0–14.8)[a]	30.1 (5.1–48.6)[a]	46.5 (29.5–64.1)	54.9 (38.2–68.6)

*p value <0.001 when compared with IR-OME using the Wilcoxon signed rank test

Increased incidence of gastric carcinoids, once thought to be of concern, have not been proven to be true. Vitamin B_{12} deficiency was thought to be a potential problem but has not been shown in well-done studies except in patients with multiple endocrine neoplasias.[17]

Several newer issues have been raised, especially in regards to infectious diseases. Pneumonia has been reported to be higher in patients on PPI (and H_2RAs) as compared to the patients not on treatment. The odds ratio for pneumonia was 1.8 compared to those not on PPI.[18] The patients in the study had multiple comorbidities, making these results difficult to interpret. Additionally, case–control studies have reported an increase in the prevalence of *Clostridium difficile* infection while on PPIs. Odds ratios from 1.3 to 5.1 for infection have been reported.[19–21] An increase in infection has not been substantiated in direct observational studies nor has the mechanism for this increase been elucidated. More importantly, the overall incidence of *C. difficile* infection in the general population is still quite low, so any small increase is unlikely to be a major clinical problem. Nonetheless, we must increase our awareness of the potential for *C. difficile* infection in patients on PPI, especially if they are on antibiotics, hospitalized, or in chronic care facilities.

A recent study reports an increase in the odds ratio for hip fractures for patients taking a PPI.[22] There was increased risk if a patient was taking a PPI long term and on more than once a day dosing.[23] The study states the multiple confounders were accounted for, including the severity and number of comorbid conditions in the comparator groups. Two other studies support this association. While the association is plausible, it has not been proven to be causal. Although the number of hip fractures is low, if confirmed, these data may affect the way we use PPIs long term particularly in patients at risk for fracture. At present, we remind patients at risk to discuss preventative measures with their primary care providers and use the lowest effective dose needed.

It is important to note that, in an observational study (N= 230) in which patients were followed while on continuous PPI, in doses of 20–160 mg/day for up to 11 years, none of the side effects above were seen.[24]

Multiple dose–response, meal, and dose timing pharmacodynamic studies reinforce the following key principles for clinical practice:

- Daytime control of intragastric pH is superior to nighttime control when PPIs are given in the morning.[25] A single daily dose given in the morning before breakfast will help most patients. A PPI given before dinner improves nighttime pH control without effect on daytime pH control.[16] Bedtime dosing of IR-OME will shift this curve to better overnight pH control compared to daytime.[14] Symptom studies are not available to compare these dose timings.

- Intragastric pH studies support superiority of acid control with twice daily dosing compared to double dose once daily in patients needing higher doses than approved by the FDA.[16]

- We recommend that all PPIs be dosed prior to meals for optimal efficacy. Our own data found superior daytime pH control (time intragastric pH >4) when PPI was taken before breakfast compared to an empty stomach.[11] Despite knowing these data, the appropriate timing of a meal is still under emphasized by clinicians. Patients often use PPIs in the morning and do not eat breakfast, taking their drug after a meal or at bedtime. A small adjustment in timing to before dinner, or eating breakfast *after* the morning dose, may improve clinical outcome. Consider IR-OME in patients needing nighttime control, especially the early hours after going to sleep.

- Optimal intragastric pH control is the key to effective treatment. Better control results in improved outcomes.[26]

Summary

PPIs are safe and effective agents for GERD. A single daily dose works for most. All available PPIs offer excellent symptom relief and healing of erosive esophagitis both short and long term. Esomeprazole 40 mg once daily offers small improvements in erosive esophagitis healing and symptom relief at 4 and 8 weeks compared to omeprazole 20 mg,[27] lansoprazole 30 mg,[28] and pantoprazole 40 mg.[29] The clinical importance of these statistical differences

continues to be debated. In practice, cost usually guides therapy. Omeprazole OTC is equal in strength to standard FDA approved dose by prescription. IR-OME offers options for patients with nighttime heartburn and off label as an on-demand PPI. Optimal efficacy of PPIs should ideally be given before a meal. Higher doses, if needed, should be given in split dose taking advantage of improved pH control when given twice daily. Careful vigilance and more studies are needed to evaluate the potential for side effects in those on long-term therapy. Until more studies are available, PPIs remain the treatment of choice for clinical management for the vast majority of patients with GERD.

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