

New Therapeutic Options in the Treatment of GERD and Other Acid-Peptic Disorders

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Presentation Summary

Gastroesophageal reflux disease (GERD), or the regurgitation of gastric content into the esophagus, is an acid-peptic disorder that has a significant impact on both health and the quality of life. Because gastric acid plays a major role in the pathophysiology of this disease, acid neutralization/suppression has emerged as the cornerstone of GERD therapy. Currently, there are 3 classes of drugs used to increase gastric pH: antacids, histamine₂ receptor antagonists (H₂RAs), and proton pump inhibitors (PPIs). Antacids act by neutralizing the pH of the stomach. However, because of their limited efficacy and short duration of action, they have not been shown to be effective in either the prevention or healing of GERD-induced esophageal injury. Moreover, numerous doses per day are often required to control GERD symptoms. A second class of agents, H₂RAs, act by inhibiting a histamine-dependent biochemi-

cal pathway that stimulates acid secretion by the gastric parietal cell. However, because there are several other stimulatory pathways that also contribute to acid secretion, a lack of consistent efficacy of H₂RAs exists among individuals. Moreover, because there are several pathways leading to acid secretion, patients who receive H₂RAs often experience tachyphylactic reactions to these drugs. The PPIs are the latest and most effective medications for the treatment of GERD. Unlike H₂RAs, PPIs block acid secretion at its source—the proton pump of the gastric parietal cell. Studies have consistently shown that PPIs are more effective than H₂RAs in resolving GERD symptoms, healing erosive esophagitis, and preventing esophageal injuries. PPIs are also effective in the treatment of acid-peptic disorders other than GERD, such as duodenal and gastric ulcers. Four PPIs are currently available in the United States: omeprazole, lansoprazole, rabeprazole, and pantoprazole.

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Gastroesophageal reflux disease (GERD) is defined as the backward flow of gastric contents into the esophagus. Although the etiology of this disease is multifactorial, the injuries associated with GERD

ultimately arise from exposure of the esophageal mucosa to gastric acid, which is present in the refluxed material. Such acid plays a pivotal role in GERD, because in addition to its corrosive properties, gastric acid also acti-

vates pepsin, a digestive enzyme that contributes to the development of esophageal mucosal injury.

Several lines of evidence show that the severity of GERD-induced injuries directly correlates with the acidity of the refluxed material and the duration of esophageal exposure to the gastric refluxate.^{1,2} Congruent with these findings, it has been observed that the healing of erosive esophagitis is promoted by increasing gastric pH.³ Thus, increasing gastric pH has become the mainstay of GERD treatment.³

Antacids—Raising the Gastric pH

Patients with infrequent heartburn often use antacids to neutralize gastric pH and relieve their symptoms. However, because antacids have a very short duration of action, patients with frequent symptoms often require numerous doses per day; moreover, antacids have not been shown either to prevent or promote the healing of esophageal injuries induced by GERD.^{4,5}

Histamine₂ Receptor Antagonists

A second class of agents used to raise gastric pH in GERD patients, the

histamine₂ receptor antagonists (H₂RAs), inhibit gastric acid secretion through the blockade of 1 of at least 3 types of cell-surface receptors on the gastric parietal cell that stimulate acid secretion.^{3,6} H₂RAs have been shown to be more effective than antacids in relieving GERD symptoms and in inducing the healing of esophageal injuries. However, their effects are not consistent, especially with regard to meal-stimulated acid secretion.^{3,6,7} Numerous doses per day are usually required to heal erosive GERD, which can reduce patient compliance and have a negative impact on the outcome of therapy.

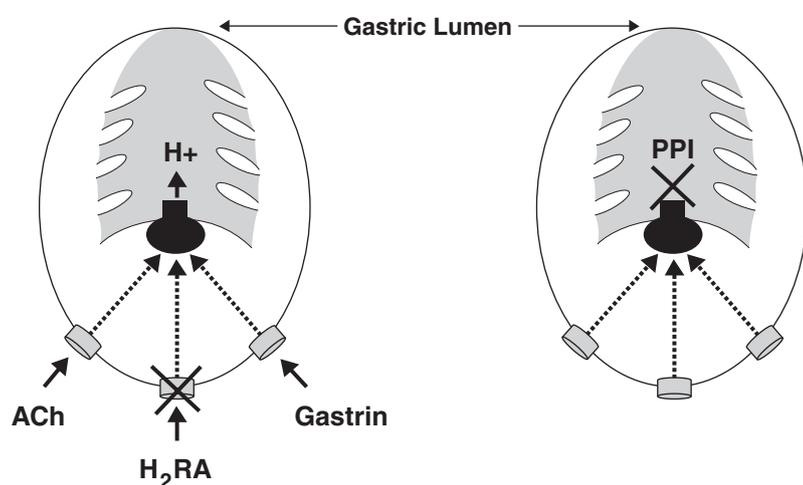
A serious drawback to the long-term use of H₂RAs is the development of tachyphylaxis, which results in the failure of mucosal injury to heal, and in early GERD, resulting in relapses during prophylactic therapy.⁷ In addition, some H₂RAs pose a risk of interaction with other drugs, and for patients with renal or hepatic disease, dosage adjustments of this drug may be necessary.^{7,8}

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) represent the most effective class of acid-suppression therapy.⁹ Four PPIs are available in the United States: omeprazole, lansoprazole, rabeprazole, and the recently approved pantoprazole. Data demonstrate that pantoprazole has an efficacy comparable to that of other PPIs and the lowest potential for drug interaction among this class.¹⁰ Currently, pantoprazole is approved in 77 countries and marketed in 63. It has been studied in more than 100 clinical trials.

Data have shown that PPIs are more effective than H₂RAs in relieving GERD symptoms, suppressing acid secretion, and promoting the healing of patients with erosive esophagitis.^{6,9,12-15} Combined with antibiotics, PPIs have also been shown to be effective in the eradication of *Helicobacter pylori*, a bacteria

Figure 1. Mechanism of Action of H₂RAs and PPIs



ACh = Acetylcholine; H₂RAs = histamine₂ receptor antagonists; PPI = proton pump inhibitor.

associated with the development of peptic ulcers.^{16,17}

Proton pump inhibitors can induce significant acid suppression, even in patients who are resistant to H₂RA therapy. One such study of 159 patients with erosive esophagitis showed that lansoprazole induced healing in 80% of the patients who were previously resistant to H₂RA therapy.¹⁴ In another study, pantoprazole induced a healing rate of 96.7% in patients who were unresponsive to high-dose H₂RA therapy.¹⁵

The difference between PPIs and H₂RAs lies in their mechanisms of action. Unlike H₂RAs, which block only 1 of several pathways that can induce acid secretion, PPIs act by binding directly to the proton pump (H⁺/K⁺ ATPase) of the gastric parietal cell.³ Because the proton pump is the final step in all biochemical pathways leading to acid secretion, PPIs are the most effective antisecretory compounds in current use (Figure 1).³ All drugs of this class block acid secretion by irreversibly inhibiting ATPase, resulting in a long duration of action. For acid production to resume, the gastric parietal cell must synthesize new proton pumps.³

Although the PPIs are similar in their mechanism of action, their binding to the proton pump occurs at different sites. The PPIs, with the exception of pantoprazole, bind to 1 of the 2 cysteine residues critical for acid inhibition (813,822), and other cysteine residues of unknown function.³ Pantoprazole is target specific in its binding; it binds to the proton pump only at cysteines 813 and 822.

PPI Pharmacokinetics/Pharmacodynamics

Of the 4 PPIs, lansoprazole has the highest bioavailability (Table). However, the presence of food in the stomach significantly decreases its absorption. Food does not play a significant role in the absorption of omeprazole, rabeprazole, and pantoprazole.¹⁸

For PPIs, in general, no dosage adjustments are necessary for elderly patients and patients with renal impairment. For patients with hepatic impairment, no dosage adjustments are required for omeprazole and pantoprazole. For patients with hepatic disease who receive lansoprazole, increases in mean area under the time/concentration curve of up to 500% were observed. Therefore, dosage adjustments of lansoprazole should be considered in patients with severe hepatic disease. For rabeprazole, there is a lack of clinical data regarding patients with hepatic impairment. Therefore, in these patients, rabeprazole should be used with caution.⁷

For Asian populations, 20% of which are slow metabolizers, no dosage adjustments are necessary for pantoprazole. In contrast, dosage adjustments of omeprazole are necessary in this population, especially in maintenance therapy.^{7,19-21}

All PPIs are metabolized through the cytochrome P450 system of liver enzymes.²⁰ Pantoprazole undergoes additional sulfate conjugation phase II metabolism, which is unique among the PPIs and contributes to its low potential for drug interactions.^{8,23,11}

Treatment of Acute GERD Symptoms

There have been numerous studies on the efficacy of PPIs for GERD symptoms. Most of these studies report symptom relief and healing of

Table. Proton Pump Inhibitors Pharmacokinetics Data

	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Bioavailability	30%-40%	>80%	52%	77%
Food Effect	None	50%↓ AUC, C _{max}	Delayed T _{max}	Delayed T _{max}

AUC = Area under the time/concentration curve.

erosive GERD. One study concluded that patients who received 30 mg of lansoprazole daily experienced less daytime heartburn than patients who received ranitidine ($P = 0.013$).²³ Another study found that of patients who received 30 mg of lansoprazole daily for 6 or 12 weeks, 2.6% experienced grade 3 (severe) heartburn, 5.2% grade 2 (moderate) heartburn, and 16.9% grade 1 (mild) heartburn. Importantly, 75.3% experienced no symptoms of heartburn.²⁴ Studies have demonstrated that pantoprazole is also effective in relieving GERD symptoms. One study showed that pantoprazole provides an advantage over ranitidine in relieving symptoms of heartburn and acid regurgitation and that reflux symptoms were similarly alleviated by pantoprazole and omeprazole.²⁵ In a study comparing placebo, nizatidine, and pantopra-

zole, pantoprazole proved effective in inducing complete resolution of daytime and nighttime GERD symptoms, in many cases from the first day of treatment.²⁶

Healing of Erosive Esophagitis

Erosive esophagitis results from the caustic effects of acid and pepsin on the esophageal mucosa, which can result in serious complications, including dysphagia, odynophagia, stricture, and bleeding.

The PPIs have been consistently shown to be superior to H₂RAs in the healing of erosive esophagitis. In a comparative study of 152 patients with erosive esophagitis, omeprazole (20 mg/day) resulted in a healing rate of 67% after 4 weeks of therapy. In contrast, ranitidine (150 mg twice a day) induced healing in only 31% of the patients ($P < 0.0001$). After 8 weeks of therapy, the healing rates were 85% and 50%, respectively ($P < 0.0001$) (Figure 2).²⁷

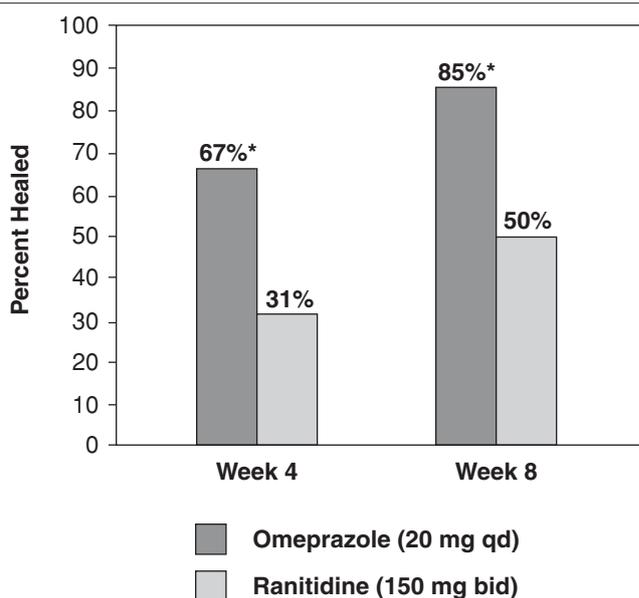
Another study compared the effects of lansoprazole with those of ranitidine on the healing of erosive esophagitis. This study showed that lansoprazole (30 mg/day) induced a healing rate of 92% after 8 weeks of therapy. Ranitidine (150 mg twice a day) induced a healing rate of 69.9% after the same period ($P < 0.001$).²⁸

Pantoprazole has also proven to be highly effective in the healing of erosive esophagitis. The data show that pantoprazole (40 mg) was more effective than the H₂RA nizatidine (150 mg bid) in healing erosive esophagitis (Figure 3).²⁶ Other studies evaluating PPI efficacy in the treatment of erosive esophagitis have demonstrated that patients who received pantoprazole had a healing rate of approximately 90% after 8 weeks of therapy.²⁹

Maintenance Therapy for GERD

Gastroesophageal reflux disease is a chronic condition that requires maintenance care.^{30,31} If acid suppression is withdrawn, GERD symptoms

Figure 2. Erosive Esophagitis Healing Rates: Omeprazole Versus Ranitidine



* $P < 0.0001$.
Source: Reference 27.

or esophageal injuries will return in the majority of patients. In comparative studies of maintenance therapy for GERD, PPIs have consistently outperformed H₂RAs in both acid suppression and the prevention of esophageal disease.^{1-6,9,13,14,24,25,33,34} In a multicenter study of 159 patients with healed esophagitis, omeprazole (20 mg/day) resulted in a remission rate of 89% during 1 year of therapy.³⁴ Healing rates for lansoprazole (30 mg/day) for a 12-month period ranged from 55% to 90%.³⁵ A 2-year follow-up study³⁴ concluded that patients who received a single daily dose of pantoprazole maintained endoscopic remission rates of 87% and 76% after 12 and 24 months, respectively.

Cost Effectiveness of PPIs in GERD Treatment

Most studies that analyzed the cost effectiveness of acid-suppression therapy have been performed in the context of GERD treatment. The consensus among these studies is that PPI therapy has a higher acquisition cost than H₂RA therapy, but its improved efficacy more than offsets its expense.^{9,37,38} In fact, PPI therapy has been found to be the most cost-effective acid-suppression therapy, especially in more severe cases of GERD because H₂RAs are disproportionately less effective than PPIs in such cases.⁹ In most situations, high-dose H₂RA therapy is the least cost effective because it is more expensive and less effective than PPI treatment.^{9,37}

Peptic Ulcer Disease

Gastric acid and pepsin also contribute to peptic ulcer disease (PUD), (duodenal and gastric ulcers). Each year approximately 500,000 new cases of PUD and 4 million cases of PUD recurrence occur in the United States.³⁹ Peptic ulcer disease is the most common cause of acute bleeding from the gastrointestinal (GI) tract. A mortality rate of 6% to 10% has been observed in patients with bleeding

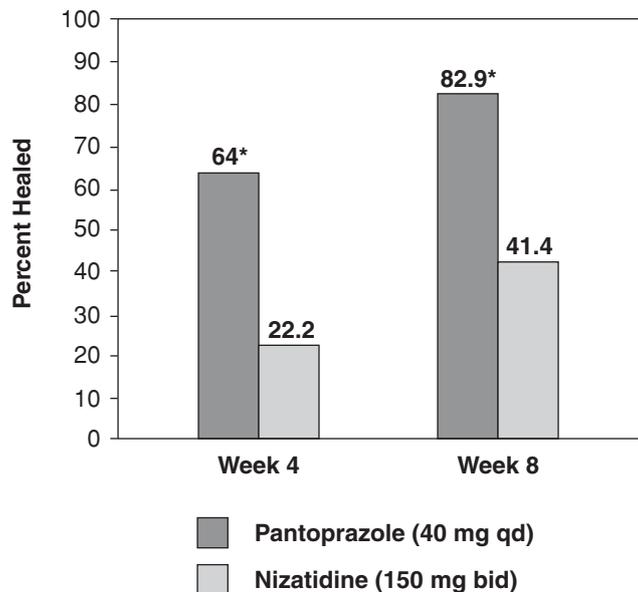
ulcers.⁴⁰ The majority of those deaths occur as a result of comorbid diseases or complications of surgery performed to stop the bleeding. In addition to its impact on overall health, PUD continues to have a significant economic effect in the United States. Acute symptoms of PUD lead to 8 million physician visits annually, as well as 275,000 hospitalizations for a yearly total of 3 million days of hospital stay.⁴¹

The pathophysiology of PUD involves a compromise of the GI mucosa that is exacerbated by the activity of acid and pepsin. *H pylori* and nonsteroidal anti-inflammatory drugs have been shown to play an important role in the development of PUD.³

Acid Suppression in PUD Healing

Numerous studies demonstrate that acid suppression is important in

Figure 3. Erosive Esophagitis Healing Rates: Pantoprazole Versus Nizatidine



*P < 0.001.

Source: Reference 26.

the healing of ulcers and that the PPI class in general is more effective than H₂RAs in this role. A study that assessed the efficacy of pantoprazole (40 mg/day) with ranitidine (300 mg/day) in the healing of acute gastric ulcers concluded that at the end of 2, 4, and 8 weeks of treatment the healing rates for the pantoprazole group were 37%, 87%, and 97%, respectively.⁴¹ In a study of 219 patients with gastric ulcers, the healing rate for patients who took pantoprazole was 88% after 4 weeks of therapy and 96% after 8 weeks. Healing rates for patients who took omeprazole were 77% after 4 weeks of therapy and 96% after 8 weeks.⁴³

Duodenal Ulcer

The findings of a multicenter study involving more than 1000 patients demonstrated that the healing rates for the treatment of duodenal ulcer with omeprazole 20 and 40 mg daily were 66% and 93%, respectively, at the end of 2 weeks, 97% and 72%, respectively, at the end of 4 weeks, and 97% and 99.8%, respectively, at the end of 8 weeks.⁴⁴ A dose escalation study has concluded that 30 mg of lansoprazole daily resulted in a healing rate of 74% at the end of 2 weeks and 95% at the end of 4 weeks.⁴⁵

Several studies have shown that pantoprazole is also effective in promoting the healing of acute duodenal ulcer.^{39,46,47} In a 1995 study, 73% of the patients who received pantoprazole experienced complete healing after the first 2 weeks, and after 4 weeks the rate increased to 92%. Patients who received pantoprazole also experienced a high rate of symptom relief.⁴⁷ Another study demonstrated that the healing rates of acute duodenal ulcers for patients who received pantoprazole were 81% after the first 2 weeks of treatment and 97% after 4 weeks of treatment.⁴⁸

PPIs in Combination With Antibiotics in the Treatment of PUD

Infection with *H pylori* is an important factor in the development of PUD. It has been estimated that this bacteria is present in 60% to 80% of gastric ulcer cases and 70% to 80% of duodenal ulcer cases.^{4,49}

The eradication of *H pylori* infection in duodenal ulcer has been achieved with a variety of antimicrobials, including amoxicillin, metronidazole, and ampicillin. Because antibiotic resistance is an issue, current approaches to *H pylori* eradication have added the macrolide clarithromycin. The PPIs play a significant role in regimens directed at the eradication of *H pylori*. Short-term therapy with any PPI, in combination with amoxicillin and clarithromycin, has resulted in very high *H pylori* eradication results.

A study performed to assess the role of omeprazole in *H pylori* eradication concluded that the eradication rate for patients who received a combination of amoxicillin (1000 mg) and clarithromycin (250 mg) twice daily was only 25%. When omeprazole (20 mg/day) was added to this regimen, the eradication rate was 95%. Patients who received a combination of metronidazole (400 mg) and clarithromycin (250 mg) twice daily experienced an eradication rate of 72% whereas those who took omeprazole (20 mg/day) in addition to this regimen experienced an eradication rate of 91%.⁵⁰

Another study showed that 15 mg of lansoprazole taken twice a day, along with amoxicillin and clarithromycin, resulted in an eradication rate of 87%.⁵¹

A comparative study of omeprazole and pantoprazole has concluded that pantoprazole (40 mg), amoxicillin (1000 mg), and clarithromycin (500 mg) taken twice daily resulted in an *H pylori* eradication rate of 93.7%.

Patients who took omeprazole with those antibiotics experienced an eradication rate of 94%.⁵²

PPI Intravenous Formulation

Pantoprazole is currently awaiting approval of its intravenous (IV) formulation. Studies in GERD patients concluded that both oral and IV formulations of pantoprazole are effective in increasing gastric pH and can be assumed to be equipotent.^{33,53} Pantoprazole IV has been shown to be significantly more effective in reducing acid output than famotidine IV.⁵³ In a study of 21 patients with Zollinger-Ellison syndrome, pantoprazole IV (80 mg/12 hours) reduced acid output to less than 10 mEq/hour—defined as effective control—in 81% of the cases for up to 7 days.⁵⁵

Summary

Of the 3 classes of drugs used to increase gastric pH—antacids, H₂RAs, and PPIs—PPIs are the most cost effective and have been found to be clinically effective in resolving GERD symptoms, healing erosive esophagitis, preventing esophageal injuries, and treating acid-peptic disorders other than GERD such as duodenal and gastric ulcers.

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