Optimizing Medical Therapy for Gastroesophageal Reflux Disease: State of the Art

Philip O. Katz, MD

Department of Medicine, Graduate Hospital, Philadelphia, PA

Potential interventions for gastroesophageal reflux disease include lifestyle modifications, antacids, mucosal protectants, prokinetic (promotility) agents, H_2 receptor antagonists (H_2RAs) and, the agents of choice in 2003, proton pump inhibitors (PPIs). This article reviews the current state of the art in use of these agents. Lifestyle changes, though sound in their intent and in many cases based on solid laboratory research, can today be considered only adjuncts to pharmacologic therapy. The mainstay of pharmacologic therapy in 2003 is antisecretory therapy. Both H_2RAs and PPIs inhibit acid secretion and raise intragastric pH. H_2RAs only block one receptor, have limited effect on acid reduction, and are relatively weak inhibitors of meal-stimulated acid secretion. PPIs provide superior control of intragastric pH over a 24-hour period compared with H_2RAs and effect greater symptom relief and healing.

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Medical therapy for gastroesophageal reflux disease (GERD) is based on our understanding of the pathophysiology of the disease and on treatment goals, which vary according to symptom presentation and organ damage. The ideal medical therapy would augment lower esophageal sphincter pressure and/or reduce the number of transient lower esophageal sphincter relaxations, accelerate esophageal clearance and gastric emptying, augment mucosal resistance, and neutralize gastric acidity. Although many of these goals are possible with

Table 1
Lifestyle Modifications for Gastroesophageal Reflux Disease

- Elevate head of bed 6 inches; avoid waterbeds
- Attempt to sleep left side down
- Modify diet
  1) Lower fat, raise protein
  2) Avoid specific irritants
     a) citrus juices
     b) tomato products
     c) coffee, tea
     d) alcohol (?)
     e) colas
  3) Do not eat prior to sleeping (allow at least 2 hours)
  4) Avoid chocolate
- Decrease or stop smoking
- Avoid potentially harmful medications
  1) Anticholinergics
  2) Sedatives/tranquilizers
  3) Theophylline
  4) Prostaglandins
  5) Calcium channel blockers
  6) Alendronate
- Take antacids or alginic acid
- Take H_2 receptor antagonists in over-the-counter doses (also may be used prophylactically)

numerous currently available agents, we are short of an ideal, one-size-fits-all, physiologically based therapy. Therefore, the clinician must use the available agents either alone or in combination, with the goals of complete symptom relief, improvement in quality of life, healing of mucosal lesions should they exist, and prevention of complications. We look forward to one day delaying progression to malignancy in the patient with Barrett's esophagus.

Potential interventions include lifestyle modifications, antacids, mucosal protectants, prokinetic (promotility) agents, H_2 receptor antagonists (H_2RAs) and, the agents of choice in 2003, proton pump inhibitors (PPIs). This article reviews the current state of the art in use of these agents.

Lifestyle Modifications

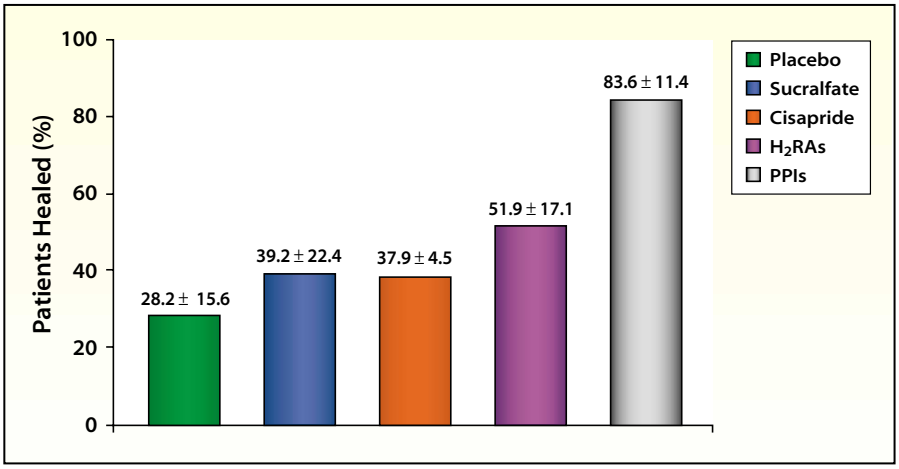
Numerous dietary and lifestyle modifications have been advocated as important in GERD therapy. Before the availability of antisecretory therapy, these interventions formed the backbone of medical therapy for this disease. However, though sound in their intent and in many cases based on solid laboratory research, these lifestyle changes (Table 1) can today be considered only adjuncts to pharmacologic therapy. Most patients have already attempted to make lifestyle changes based on their own experience of which behaviors and dietary indiscretions exacerbate their disease.

Although guidelines from the American College of Gastroenterology recommend lifestyle changes as adjuncts to treatment,[1] other experts believe that such changes play a minimal to no role in the treatment of GERD. Patient education regarding the potential of lifestyle modifications, such as sleeping on their left side and going to bed on an empty stomach to reduce symptoms, takes little time and ultimately will help some patients. However, in the absence of "hard data," it is difficult to emphasize any real efficacy associated with these interventions.

Pharmacologic Therapy: Antacids, Sucralfate, and Promotility Therapy

The mainstay of pharmacologic therapy in 2003 is antisecretory therapy.

Figure 1. *A meta-analysis of more than 2000 patients from multiple trials assessing 4–12-week healing rates in patients with erosive esophagitis treated with placebo, sucralfate, cisapride, H_2 receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs) showing the clear superiority of PPIs in healing of erosive esophagitis. Adapted from Chiba et al.*[2]



However, the clinician needs to be familiar with the mechanisms of action and efficacy data of antacids, sucralfate, and prokinetic agents, because they are more widely used than one might expect. Healing rates of the available agents are displayed in Figure 1.[2]

Antacids

These over-the-counter agents are widely used by patients with heartburn who self-medicate and never seek further treatment for their symptoms. Evidence suggests that many patients will use antacids to supplement other antisecretory therapy. Antacids and alginic acid are more effective than placebo in the relief of heartburn, and combined antacid and alginic acid therapy may be superior to antacids alone in the control of symptoms. In high doses, these agents are no more effective at healing erosive esophagitis than placebo and are most effective when given in the first hour after a meal.[3,4]

In high doses, antacids are no more effective at healing erosive esophagitis than placebo.

Sucralfate

The only mucosal protective agent, sucralfate binds to inflamed tissue. It may block diffusion of gastric acid and pepsin across the mucosal barrier and inhibit the erosive action of pepsin and bile.[5] Head-to-head comparisons of sucralfate and H_2RAs demonstrate equivalent healing of erosive esophagitis, although overall healing rates are not as high with sucralfate (Figure 1).[6,7] Constipation is seen in 2% of patients. Little use remains for this compound in modern medical therapy for GERD, outside of therapy for pregnant patients. Little systemic absorption of the agent is seen, so it is likely safe for this population.

Promotility Therapy

Promotility or motility-altering agents include cisapride, metoclopramide, domperidone, and tegaserod. Conceptually, such agents might present the ideal therapy for GERD. Addressing the underlying pathophysiologic defects of the lower esophageal sphincter, augmenting esophageal clearance, and increasing gastric emptying would constitute a nearly ideal therapy. Unfortunately, cisapride has essentially been withdrawn from the market owing to side effects (principally cardiac), and metoclopramide, the remaining agent available in this country, has limited therapeutic efficacy and an unfavorable side-effect profile.

Metoclopramide crosses the blood–brain barrier and interacts with dopamine receptors, producing clinically important central nervous system side effects, such as drowsiness and confusion.[8] Clinical trials have found equivalent efficacy of metoclopramide compared with H_2RAs in relieving heartburn and other GERD symptoms.[9–11] At a dose of 10 mg four times daily, it is more effective than placebo in improving symptoms[12,13]; however, it has never been shown to be more effective than placebo in healing of erosive esophagitis. Anxiety, agitation, confusion, motor restlessness, hallucinations, and drowsiness are common, seen in up to 20%–30% of patients. Depression and potentially irreversible tardive dyskinesia are the most serious side effects. Adverse effects appear to be dose-related and are more frequent in the elderly. If there is a use for this agent in GERD, it is in patients with documented gastroparesis or scleroderma.

Seen in up to 20%–30% of patients, anxiety, agitation, confusion, motor restlessness, hallucinations, and drowsiness are common side effects of metoclopramide.

Domperidone, a dopamine antagonist, is available outside the United States and in several U.S. pharmacies that compound the drug.[14] It does not cross the blood–brain barrier, so has few of the central dopaminergic side effects of metoclopramide. It should not be administered with antisecretory agents or antacids because reduced gastric acidity may impair its absorption. Efficacy studies suggest similarity to H_2RAs (ranitidine and famotidine) in symptom relief and in promotion of esophageal healing.[15,16] Hyperprolactinemia, nipple tenderness, galactorrhea, and amenorrhea are the most common side effects of this agent, which is unlikely to be approved in the United States.

Tegaserod, a selective partial 5-HT4 agonist, has recently been approved in the United States for treatment of constipation-predominant irritable bowel syndrome. Its promotility effects suggest reason to study this agent in disorders of gastric emptying and perhaps GERD, although no substantial clinical trials have been conducted to date.[16]

Prokinetic agents have historically fallen short of expectations. In their current form, in the era of potent antisecretory therapy, they should

play little role in the management of the patient with GERD.

Pharmacologic Therapy: Acid-Suppressive Therapy

Antisecretory agents are the drugs of choice for pharmacologic treatment of GERD. Two classes of acid-suppressive agents are available: H_2RAs and PPIs. An understanding of their mechanisms of action and efficacy is crucial to optimal use of these agents either alone or in combination. Therefore, following a review of acid production, a discussion of the mechanism of action and efficacy of these agents is presented.

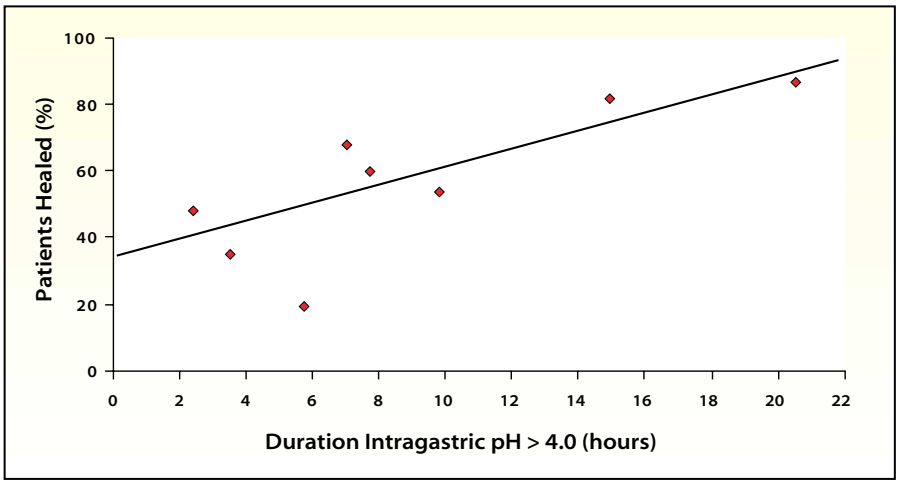


Figure 2. *Meta-analysis of treatment trials of endoscopically assessed erosive esophagitis healing rates showing a strong correlation between the number of hours in a day that the intragastric pH is above 4 and healing of erosive esophagitis. Data from Bell et al.*[17]

Acid Production

Parietal cells are located within the mucosa, predominantly in the body of the stomach. They produce an average of 2 L of gastric acid per day. Located on the basal lateral membrane of the parietal cell are receptors for three substances that stimulate acid secretion: gastrin, acetylcholine, and histamine. Gastrin, present in the G cells in the gastric antrum, is stimulated by the presence of food in the stomach (gastric phase of acid secretion) and reaches the parietal cell via the blood. Acetylcholine is released from the vagus nerve, predominantly during the cephalic phase of acid secretion, that is, the sight, sound, smell, and taste of food. Release of either of these substances stimulates the enterochromaffin-like cell to release histamine, which binds to its receptors on the parietal cell. Activation of these receptors stimulates intracellular protein phosphokinase (cyclic adenosine 3',5' monophosphate), which acts as a second messenger to stimulate the proton pump, which is in a resting, inactive state in the tubulovesicle. Stimulation of the pump configures it into its active form at the secretory canaliculi, where it exchanges a hydrogen for a potassium ion through the hydrogen potassium ATPase enzyme, the final step in acid secretion. Inhibition of any of the receptors on the basal lateral membrane will inhibit acid production to some degree, whereas inhibition of the proton pump inhibits the final common pathway, thus creating the opportunity for superior acid suppression.

Agents that raise intragastric pH to greater than 4 for the longest period have the greatest potential to provide symptom relief and mucosal healing in patients with GERD.

Both H_2RAs and PPIs inhibit acid secretion and raise intragastric pH. The number of hours of the day for which these agents raise intragastric pH to greater than 4 is an indirect measure of efficacy of symptom relief, correlates with healing of erosive esophagitis, and is important in understanding efficacy data. When gastric pH is less than 4, pepsinogen is activated to pepsin, which can exacerbate esophageal damage caused by acid. A meta-analysis has linked healing of erosive esophagitis to the duration of time (over a 24-hour period) that the intragastric pH is less than 4 (Figure 2).[17] Agents that raise intragastric pH to greater than 4 for the longest period have the greatest potential to provide symptom relief and mucosal healing in patients with GERD.

H_2RAs

The four available H_2RA agents, cimetidine, ranitidine, famotidine, and nizatidine, derive their efficacy in GERD exclusively by inhibition of acid secretion. H_2RAs block only one receptor, have limited effect on acid reduction, and are relatively weak inhibitors of meal-stimulated acid secretion, reducing it by at most 60%–70% for only about 8 to 10 hours.[17,18] The antisecretory capabilities of H_2RAs are best at night, with duration of acid inhibition longer when the drug is taken in the evening or before bedtime. Equipotent doses of all H_2RAs inhibit acid secretion

equally; thus, all four agents have similar efficacy in managing GERD. H_2RAs were made available as over-the-counter agents in 1995.

Symptom relief has been variable, ranging from 32%–82% of patients, with endoscopic healing in as few as 0 patients to as many as 82%.[19] In a later meta-analysis, endoscopic improvement was demonstrated in 31%–88% of patients, with complete healing seen in 27%–45% of patients who had primarily grade I or II lesions.[20] Standard-dose H_2RAs are often recommended as the first choice for treatment in many step-up algorithms. Higher doses of H_2RAs given either twice or four times a day may increase efficacy. Although non–placebo-controlled, comparative studies have produced 12-week rates as high as 80%, these rates are unusual in practice and when higher grades of erosive esophagitis are treated.[21–26] Although higher doses are recommended in step-up algorithms, expectations for efficacy of higher doses may be overestimated in patients with severe disease, requiring greater acid suppression (see discussion under "Step Therapy" below).

Overall, as a class, the H_2RAs are extremely safe, with side effects seen in 4% of patients or less. Typically, minor gastrointestinal side effects, such as nausea, abdominal pain, and bloating, are seen and are of little clinical concern. There have been concerns about drug interactions with H_2RAs (cimetidine in particular), particularly interactions with agents affecting the cytochrome P450 system. Serum concentrations of phenytoin, procainamide, theophylline, and warfarin have been altered after administration of cimetidine, and to a lesser degree ranitidine; these effects are not seen with famotidine and/or nizatidine.[27,28] However, the consequence of these interactions is rarely clinically important. Nevertheless, awareness of these potential complications needs to be considered if H_2RAs are prescribed. The possibility of mental confusion, particularly with the intravenous use of these agents, must be considered if they are used in the hospital setting.

PPIs

PPIs are clearly the most effective agents available for the treatment of GERD. They provide superior control of intragastric pH over a 24-hour period compared with H_2RAs and effect greater symptom relief and healing. Inhibiting the final common pathway of acid secretion, these agents suppress daytime, nighttime, and meal-stimulated acid secretion to a significantly greater degree than do H_2RAs.[29] There are five PPIs currently available: omeprazole, lansoprazole, rabeprazole, pantoprazole and, the newest, esomeprazole, the s-isomer of omeprazole. PPIs are weak bases that concentrate in the secretory canaliculi at acidic pH. Highly selective, they can concentrate up to 1000-fold in the acidic environment of the canaliculi. The inactive benzimidazole of the PPI is converted to a cationic sulfonamide, which binds to cysteines on the proton pump, blocking acid-producing capabilities.[30,31] PPIs bind covalently and irreversibly to proton pumps; therefore, the degree of inhibition is related to area under the curve, not plasma concentration. PPIs block 70%–80% of active pumps; therefore, for acid secretion to resume, new hydrogen potassium ATPase molecules must be synthesized, a process that takes 36 to 96 hours. Each agent has subtly different binding capabilities; however, maximal efficacy in control of intragastric pH occurs when the drugs are taken before a meal, as the drugs bind to actively secreting pumps. It is recommended that PPIs be administered before the first meal of the day and, when a second dose is needed, before the evening meal rather than at bedtime. Not all pumps are active at any given time; thus, a single dose of a PPI does not inhibit all pumps and, therefore, does not completely inhibit all acid secretion. Acid inhibition is never complete because of the continued synthesis of new pumps, and a steady state is required in order to maintain continuous acid control. When PPIs are administered twice daily, more active pumps are exposed to the drug, and the steady-state inhibition of gastric acid is more rapidly achieved and will be more complete.

Intragastric pH control. The increase in pH control over a 24-hour period accounts for the superiority of PPIs over H_2RAs. Omeprazole, lansoprazole, pantoprazole, and rabeprazole are similar in their control of intragastric pH, as demonstrated in several studies and highlighted in a comparison study of all four from our laboratory.[32] A randomized, five-arm crossover study compared 24-hour intragastric pH control in GERD patients receiving omeprazole, 20 mg; lansoprazole, 30 mg; rabeprazole, 20 mg; pantoprazole, 40 mg; and esomeprazole, 40 mg. A 2-week washout period was required between treatments. Esomeprazole, 40 mg, was superior to the other PPIs in 24-hour pH control in over 80% of subjects (Figure 3).[33]

Clinical efficacy: symptom relief. The success of a drug used to treat GERD is measured by its ability to relieve symptoms and effectively heal erosive esophagitis. Overall, a once-daily morning dose of a PPI is highly effective in relief of symptoms and heals erosive esophagitis in 78%–95% of patients (Figure 1).[2] Highlights of key comparative clinical trials are presented below.

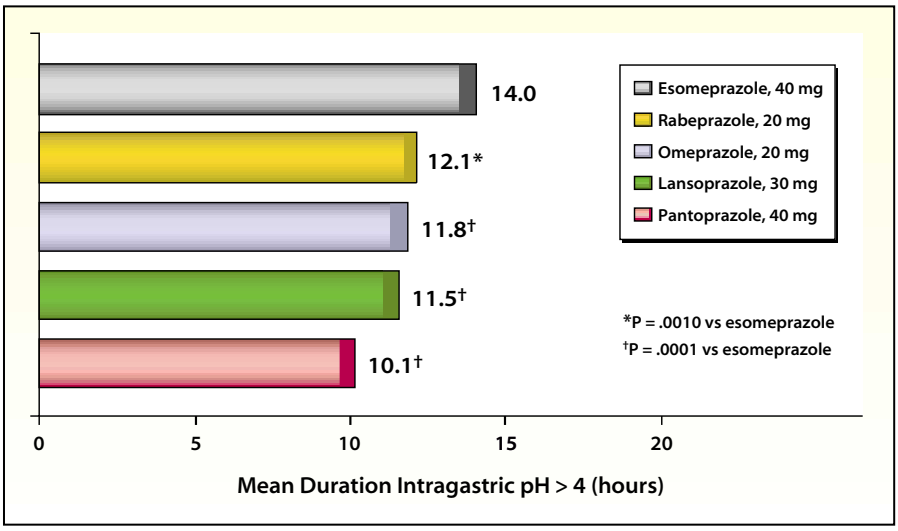


Figure 3. *Five-arm crossover study (N = 34) comparing intragastric pH control in patients with symptoms of GERD taking omeprazole, 20 mg; lansoprazole, 30 mg; pantoprazole, 40 mg; rabeprazole, 20 mg; and esomeprazole, 40 mg.*

Although all PPIs provide a high level of symptom improvement, there are some variations in PPI performance when compared head to head. Castell and colleagues[34] compared efficacy and safety of lansoprazole, 15 or 30 mg once daily; omeprazole, 20 mg once daily; and placebo in approximately 1300 patients with grades II–IV erosive esophagitis. Daytime and nighttime relief of heartburn with all active treatments was statistically superior to that with placebo. The 30-mg dose of lansoprazole was slightly more effective than the 20-mg dose of omeprazole in speed of heartburn relief. After 8 weeks, patients receiving omeprazole reported heartburn on 12% of days and 9% of nights compared with 9% of days and 6.5% of nights ($P < .05$) for those receiving 30 mg lansoprazole.[34]

In a large (N = 3500) comparison study, Richter and colleagues[35] demonstrated superiority of lansoprazole, 30 mg, compared with omeprazole, 20 mg, in sustained resolution of heartburn (84% vs 83%; $P < .05$) after 8 weeks of treatment. A study comparing symptom relief with pantoprazole, 40 mg, versus omeprazole, 20 mg, found no statistically significant difference (94% vs 90%; P = ns).[36] A study comparing symptom relief (improvement in heartburn at 8 weeks) with rabeprazole, 20 mg, versus omeprazole, 20 mg, showed no statistically significant difference (87% vs 82%; P = ns).[37]

A large study by Castell and colleagues[38] (N = 5241) compared investigator-assessed heartburn relief with esomeprazole, 40 mg, versus lansoprazole, 30 mg. After 4 weeks, statistical superiority was demonstrated for esomeprazole (62.9% vs 60.2%; $P < .05$). A study (N = 2375) comparing esomeprazole, 40 mg, with omeprazole, 20 mg, assessed sustained resolution of heartburn (defined as 7 consecutive days with no heartburn) and found statistical superiority for esomeprazole over omeprazole at both 4 weeks and 8 weeks ($P = .001$).[39]

Clinical efficacy: healing of erosive esophagitis. A more objective measure of efficacy in drug–drug comparisons than symptom relief is healing of erosive esophagitis. PPIs produce a healing rate of approximately 11.7% of patients per week, superior to H_2RAs (5.9%) and placebo (2.9%).[33] The comparison studies related to symptom relief discussed above show no difference in healing of erosive esophagitis when lansoprazole, pantoprazole, and rabeprazole are compared with omeprazole.

Esomeprazole, the s-isomer of omeprazole, is the first PPI to show a statistical advantage in healing rates over omeprazole. The first study to demonstrate this advantage was a randomized, double-blind, controlled trial (N = 1960) comparing healing of erosive esophagitis with 20 mg of omeprazole versus 20 mg and 40 mg of esomeprazole daily for 8 weeks.[40] Healing rates were statistically superior for esomeprazole compared with omeprazole at both 4 and 8 weeks. A second study[39] (N = 2425) confirmed these findings. Of interest is the finding that the healing rate of erosive esophagitis decreases as the grade of erosive esophagitis increases. The decrement in healing seen with omeprazole was greater than that seen with esomeprazole, 40 mg.

The large clinical trial by Castell and colleagues[38] (N = 5241) compared esomeprazole, 40 mg, with lansoprazole, 30 mg. Healing rates were statistically superior for esomeprazole, 40 mg, compared with lansoprazole, 30 mg (92.6% vs 88.8%; $P < .01$), with the difference most demonstrable at the higher grades of erosive esophagitis. However, the magnitude of the difference was smaller than in the omeprazole trials. The reason for this difference in magnitude is not clear. Overall, esomeprazole, 40 mg, exhibits a 4%–8% superiority in healing compared with omeprazole and lansoprazole and effects the greatest healing in those with "more severe erosive esophagitis" (Los Angeles classification grades C and D), underscoring the importance of intragastric pH control in the healing

of erosive esophagitis.

Dose response. It is common practice to increase the dosage of PPIs if symptoms are not relieved. Whether this dosage increase will effectively increase healing of erosive esophagitis is difficult to demonstrate in clinical trials. In Castell's study,[34] discussed above, 15 mg of lansoprazole daily resulted in a healing rate of 79%, whereas 30 mg of lansoprazole resulted in a healing rate of 91%. A similar dose-dependent pattern was demonstrated by Lundell and colleagues,[41] who compared 10-mg and 20-mg doses of omeprazole in healing of Los Angeles grades A to C erosive esophagitis. With the lower dose of omeprazole, efficacy in healing correlated with grade of esophagitis (77% healed with grade A, 50% with B, and 20% with C). This correlation did not occur with the 20-mg dose, which healed equivalent percentages of patients with grades A and B (80%), though a lower percentage of patients with grade C (40%). These studies suggest that there is some dose response with PPIs. However, Sontag and associates[42] compared 20-mg and 40-mg doses of omeprazole with placebo in 230 patients with erosive esophagitis grades II–IV. At week 8, there was no difference in healing overall between the 20-mg and 40-mg groups (73.5% and 74.7%, respectively). The 40-mg dose resulted in faster symptom relief; however, no difference in overall symptom relief was observed at the end of 8 weeks. Similar studies have shown no improvement in healing with 60 mg versus 30 mg of lansoprazole or 40 mg versus 80 mg of pantoprazole given once daily. In a long-term observational study, Klinkenberg-Knol and colleagues[43] showed that, by increasing omeprazole dose as needed, almost all patients refractory to ranitidine could be effectively healed.

Optimization of Medical Therapy for GERD

All available PPIs are approved for once-daily dosing. Although food affects the bioavailability of each molecule differently, it is recommended that all PPIs be given before a meal. This recommendation is based on the concepts previously discussed and on results of an intragastric pH study addressing this issue. In this two-armed crossover study, healthy subjects received omeprazole, 20 mg, or lansoprazole, 30 mg, at 8 am daily for 7 days, with the dose given either 15 to 30 minutes before the breakfast meal or on an empty stomach with no food until lunchtime. Intragastric pH monitoring was performed on day 7. A significant superiority in daytime pH control (time intragastric pH > 4) was found when the PPI was taken before breakfast versus on an empty stomach.[44] Although optimal timing has not been determined, PPIs should be taken on an empty stomach and followed by a meal.

Although optimal timing has not been determined, PPIs should be given on an empty stomach and followed by a meal.

Many patients, including those with extraesophageal symptoms and Barrett's esophagus, are treated with higher doses of a PPI. In this case, splitting the dose for twice-daily administration, before breakfast and dinner, provides superior intragastric pH control, particularly at night, compared with a higher dose given once daily. This finding was first reported in a study of healthy subjects randomized and crossed over to omeprazole, 40 mg before breakfast, 40 mg before dinner, or 20 mg twice daily (before breakfast and dinner), with a 1-week washout period between 24-hour intragastric pH measurements.[45] The most important observation of the trial was that a 20-mg, twice-daily dose was superior to the others for 24-hour intragastric pH control. A subsequent crossover study, which evaluated overnight pH control in subjects assigned to the same three treatment arms, confirmed this observation.[46] Control of daytime pH was similar regardless of regimen; however, nocturnal pH control was significantly improved with the twice-daily regimen compared with the double dose once daily. Interestingly, the 40-mg dose given before dinner was more effective at controlling intragastric pH than was the morning dose. A similar observation was reported in a study comparing rabeprazole, 20 mg, given before the morning meal versus the evening meal.[47] Intragastric pH control was better with the evening dose.

Another observation from intragastric pH studies is that of wide intersubject variability in intragastric pH control despite similar dosing regimens. One crossover study compared 24-hour intragastric pH control in healthy subjects who received omeprazole, 20 mg, or lansoprazole, 30 mg, twice daily for 7 days. Both intersubject and intrasubject variability in pH response were seen.[48] A second crossover study compared esomeprazole, 40 mg; omeprazole, 20 mg; lansoprazole, 30 mg; rabeprazole, 20 mg; and pantoprazole, 40 mg, once daily in patients with GERD symptoms; marked variability in response was seen among subjects.[32] This intrasubject variability in intragastric pH control is not easy to explain but should be taken into account when considering a switch

from one PPI to another after one seemingly fails.

Step Therapy

As our understanding of GERD and its treatment has evolved, so has our choice of therapy. Once the dominant strategy, step therapy, which involves lifestyle modifications and over-the-counter antacids followed by prescription H_2RAs and finally PPIs, is often preferred (or mandated) in treatment algorithms, particularly by managed care. In general, it falls short of optimal treatment.

This strategy was evaluated in a study by Howden and associates[49] in 593 patients randomized to the following treatment arms: 1) ranitidine, 150 mg twice a day for 8 weeks, followed by lansoprazole, 30 mg daily for 12 weeks (step up); 2) lansoprazole, 30 mg daily for 8 weeks, followed by ranitidine, 150 mg twice a day for 12 weeks (step down); 3) continuous ranitidine, 150 mg twice a day for 20 weeks; or 4) continuous lansoprazole, 30 mg daily for 20 weeks. At the end of 20 weeks, the percentage of heartburn-free days was greatest for continuous lansoprazole compared with any other strategy.

Another trial compared high-dose and standard-dose ranitidine therapy in patients initially unresponsive to 6 weeks of therapy with ranitidine, 150 mg twice daily. Four hundred eighty-one patients with GERD symptoms initially received a 6-week course of ranitidine, 150 mg twice daily. Sixty percent remained symptomatic and were randomized to receive either 150 mg or 300 mg of ranitidine twice daily. After 8 additional weeks of therapy, 45% of patients on the lower dose of ranitidine and 44.8% on the higher dose had mild or no heartburn. This study suggests that there is a peak in efficacy of H_2RA therapy regardless of dosage and duration of therapy.[40] There is no role for double-dose H_2RAs in the routine treatment of GERD.

Step-down therapy has been advocated. A recent study by Inadomi and colleagues[50] examined the feasibility of step-down therapy in patients with nonerosive GERD who were asymptomatic on PPIs. After baseline demographic and quality-of-life information was obtained, the patients were withdrawn from PPIs in a stepwise fashion. Fifty-eight percent of patients were asymptomatic following discontinuation of treatment after 1 year of follow-up. Thirty-four percent required H_2RAs, 7% required prokinetic agents, 1% required both, and 15% remained asymptomatic without medication. Although quality of life was not significantly different, management costs decreased by 37%. Younger age and heartburn were the predominant factors predicting unsuccessful PPI step-down management, suggesting that individuals with "true GERD" will fail step-down therapy.

Nocturnal Gastric Acid Breakthrough with PPIs: A Pharmacologic Phenomenon of Potential but Variable Clinical Importance

Studies using intragastric pH monitoring have shown that 70% of subjects will experience intragastric pH less than 4 for at least 1 continuous hour in the overnight monitoring period (10:00 PM–6:00 AM) even when taking twice-daily PPIs.[51] This pharmacologic phenomenon, termed nocturnal gastric acid breakthrough (NAB), begins approximately 6 to 7 hours after the evening dose of a PPI.[51] When PPIs are given once daily before breakfast, NAB occurs earlier in the evening, beginning around 11:00 PM.[32] This is a class effect, and has been demonstrated in healthy subjects as well as patients with uncomplicated GERD, Barrett's esophagus, and scleroderma.[52] Hundreds of patients treated with once- or twice-a-day omeprazole, lansoprazole, rabeprazole, and pantoprazole, have demonstrated a consistent frequency of gastric acid recovery regardless of PPI. Preliminary studies with esomeprazole suggest a decrease in the frequency of nocturnal gastric acid recovery, but this finding requires more intense study.[53]

Up to 50% of patients with Barrett's esophagus will have increased overnight esophageal acid exposure during NAB and may be asymptomatic.

Esophageal reflux occurs during nocturnal breakthrough of intragastric pH in only 5% of healthy subjects and about 15% of patients with uncomplicated GERD.[52] This observation is consistent with that from clinical trials that nocturnal heartburn is infrequent (10%–15%) on a once-a-day PPI. Symptom frequency during these nocturnal gastric pH drops has not been systematically studied but appears to be low. Overnight gastric acid recovery may be of importance in some patients with severe erosive esophagitis or Barrett's esophagus, as up to 50% of patients with Barrett's esophagus will have increased overnight esophageal acid exposure during NAB and may be asymptomatic.[54,55]

NAB is *not* due to PPI resistance, which is, in fact, an extremely rare phenomenon. Patients may appear resistant to PPIs because of the intersubject variability seen with these agents; however, intragastric pH control can usually be improved by increasing the PPI dose. One study found that six of seven patients who

appeared resistant to omeprazole, 20 mg twice a day, had improved intragastric pH control when the dosage was increased to 40 mg twice a day, reinforcing the observation that true PPI resistance is extremely rare.[56]

Combination Therapy: PPIs and H_2RAs

Most patients will have little or no reflux during periods of NAB; however, those few who do may be at risk for nocturnal symptoms or esophageal damage. The use of nocturnal H_2RAs has been popularized as a way of controlling NAB. Data are based on short-term studies, usually of 7 days' duration. Two recent articles report the results of longer-term use of nocturnal H_2RAs in conjunction with PPIs to evaluate the control of intragastric pH and raise important issues regarding long-term efficacy.

Fackler and associates[57] prospectively studied 23 healthy volunteers and 20 GERD patients examined at baseline with omeprazole, 20 mg twice daily (before breakfast and dinner) for 2 weeks, followed by the addition of an H_2RA (ranitidine, 300 mg) at bedtime for 28 days. Ambulatory pH monitoring was performed after days 1, 7, and 28 of continuous H_2RAs at bedtime.

The median time that pH was less than 4 for the overnight period was similar between patients and volunteers; therefore, the two groups were considered together. Four patterns of gastric pH response were observed. The first group experienced a decreasing effect of baseline H_2RA over time (tolerance). The second group consisted of 21% who exhibited a sustained response to H_2RA therapy (no tolerance). The third group had no NAB on PPI twice daily and remained so when H_2RA was added. All in this group were *Helicobacter pylori* positive. The fourth group was marked by an unpredictable response (26%). This group showed variable outcome at different time points in the study.

Xue and colleagues[58] retrospectively reviewed prolonged ambulatory pH monitoring studies in patients comprising two groups. Group 1 consisted of 60 patients, taking either omeprazole, 20 mg, or lansoprazole, 30 mg, twice a day. Group 2 consisted of 45 patients, taking PPI twice a day (omeprazole, 20 mg, or lansoprazole, 30 mg) plus an H_2 blocker at bedtime (ranitidine, 300 mg; famotidine, 40 mg; or nizatidine, 300 mg) for more than 28 days. A third group (n = 11) consisted of patients who were evaluated with both regimens. Percent time that nocturnal and daytime intragastric pH was greater than 4 and percent of patients with NAB were evaluated.

Twenty-seven percent of patients spent 100% of the recumbent period with intragastric pH greater than 4, 32% with greater than 90% of recumbent period greater than 4, with the remainder scattered at varying degrees. This was superior to PPI twice a day ($P < .001$). In patients tested on both regimens, median percentage time with intragastric pH greater than 4 overnight increased from 54.6% without H_2RA to 96.5% with H_2RA Hs ($P = .001$).

These two studies come to differing conclusions: the former concludes

Main Points

- Dietary and lifestyle modifications have been advocated as important therapies for gastroesophageal reflux disease (GERD); although sound in their intent and in many cases based on solid laboratory research, these lifestyle changes can today be considered only adjuncts to pharmacologic therapy.
- In the era of potent antisecretory therapy, promotility agents should play little role in the management of the patient with GERD.
- Both H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) inhibit acid secretion and raise intragastric pH; the number of hours of the day for which these agents raise intragastric pH to greater than 4 is an indirect measure of efficacy of symptom relief, correlates with healing of erosive esophagitis, and is important in understanding efficacy data.
- Symptom relief with H_2RAs has been variable, ranging from 32% to 82% of patients, with endoscopic healing in as few as 0 patients to as many as 82%; in a meta-analysis, endoscopic improvement was demonstrated in 31%–88% of patients, with complete healing seen in 27%–45% of patients who had primarily grade I or II lesions.
- The increase in pH control over a 24-hour period accounts for the superiority of PPIs over H_2RAs; omeprazole, lansoprazole, pantoprazole, and rabeprazole are similar in their control of intragastric pH.
- Overall, a once-daily morning dose of a PPI is highly effective in relief of symptoms and heals erosive esophagitis in 78%–95% of patients.
- Nocturnal gastric acid breakthrough (NAB) is not due to PPI resistance, which is a rare phenomenon; esophageal reflux occurs during NAB in only 5% of healthy subjects and approximately 15% of patients with uncomplicated GERD.

that there is no sustained control of intragastric pH over time with the addition of an H_2RA (ie, tolerance develops), and the latter concludes that there is substantial benefit to the long-term use of these agents at bedtime. Careful evaluation of these studies suggests many similarities. In the Fackler and associates study, 21% of subjects had a sustained response, which is remarkably similar to the 27% in the Xue and associates study. The absence of statistical improvement in the Fackler et al study (P = .06 at 1 week, P = .08 at 1 month) may represent a type II error. Both studies identify a substantial number of patients who have a sustained effect and many who do not. Both agree that achieving total acid control (100% time that intragastric pH is greater than 4) is extremely difficult. Whether the newest PPI, esomeprazole, 40 mg twice daily, will make this control possible awaits further study.

Fortunately, this degree of pharmacologic control is rarely necessary. It is reasonable to conclude that tolerance to H_2RAs at bedtime is real but relative, and that a sustained response may be seen in a large number of patients. Studies underscore the importance of prolonged ambulatory pH monitoring as a means of documenting acid control and avoidance of using H_2RA at bedtime empirically in difficult-to-treat patients.

Summary

Optimal therapy for GERD patients requires an understanding of the pathogenesis of the disease, awareness of the goals of long-term complete resolution of symptoms, improvement in quality of life, and prevention of complications. Antisecretory therapy is the mainstay of treatment, with PPIs the class of choice. An understanding of the steps involved in acid production, mechanisms of action of H_2RAs and PPIs, and the most effective dosing strategies will allow clinicians to effectively treat their patients. ■

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