Importance of pH Control in the Management of GERD

Richard H. Hunt, MD

The degree of esophageal mucosal injury that occurs in patients with gastroesophageal reflux disease depends on duration of exposure and pH of the refluxate. Evidence suggests that an intraesophageal pH of less than 4.0 directly correlates with the degree of mucosal injury. The advent of acid secretory inhibitors such as the histamine2-receptor antagonists (H2RAs) and, more recently, the proton pump inhibitors (PPIs) has revolutionized the treatment of patients with reflux disease. However, the evidence linking the degree of mucosal damage to pH of the refluxate has prompted investigators to reevaluate the effectiveness of these agents. The PPIs are significantly more effective than the H2RAs in achieving and sustaining an intragastric pH above 4.0. The results of clinical trials performed with the PPIs indicate a faster rate of healing of erosive esophagitis and of symptom relief than treatment with H2RAs.

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Our understanding of pathophysiology in patients with acid-related disorders has expanded substantially in recent years with the identification of Helicobacter pylori as an infectious and curable cause of most ulcers not related to nonsteroidal anti-inflammatory drug use. However, the treatment of patients with gastroesophageal reflux disease (GERD) has remained less than ideal. Despite a choice of agents that includes motility drugs, antacids, and antisecretory drugs, a substantial proportion of patients with GERD continue to be inadequately treated, to experience symptoms, and to develop GERD-related complications.

Although investigators agree that GERD is associated with dysmotility and results from an imbalance between normal defensive factors, including those of the mucosal defenses, esophageal clearance, lower esophageal sphincter (LES) tone, and aggressive factors such as acid and pepsin, it is increasingly clear that the key to controlling symptoms and to healing erosive esophagitis is to decrease the duration of exposure to the acidic refluxate. This is best achieved by increasing the intragastric pH to above 4.0 for the longest duration possible. This article reviews the epidemiology and pathophysiology of GERD and postinjury regeneration of the esophageal mucosa and discusses the most commonly used antisecretory drugs with respect to their effectiveness in controlling intragastric pH and its relationship to mucosal healing and control of symptoms.

EPIDEMIOLOGY

Because of the spectrum and variation in symptoms, a true estimate of the prevalence of GERD is difficult. Heartburn, the hallmark of GERD, is experienced by up to 11% of the general population on a daily basis, and symptoms occur in a third of the population every 3 days. Moreover, two thirds of the population experience dyspepsia at sometime in their life, approximately one third have had dyspepsia in the last 6 months, and most patients with dyspepsia also complain of heartburn.

The prevalence of GERD-related symptoms, extent of mucosal injury, and incidence of Barrett esophagus increase with age. In elderly patients, women are more frequently affected by reflux symp-

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The pathophysiology of GERD is multifactorial and depends on disruption of the complex interplay between the normal defensive mechanisms and aggressive factors. In general, GERD results when normal esophageal clearance and mucosal defensive mechanisms in susceptible individuals fail to prevent or minimize exposure of the mucosa to aggressive acidic refluxate from the stomach.

The most critical factors in the pathogenesis of GERD-related symptoms are the LES tone, frequency and duration of transient LES relaxations, acidity of the gastric contents, and amount of time that acid remains in the esophagus. In contrast to healthy subjects, patients with GERD have more frequent transient LES relaxations, which permit a reflux of gastric contents into the esophagus. Relaxation of the LES may also result from drug therapy, including calcium channel blockers, anticholinergic agents, narcotics, estrogens, and nitrates; certain foods, including chocolates, peppermint, and fatty foods; caffeine; or smoking.

A hiatal hernia displaces the LES from its normal position, altering the anatomic barrier to reflux in some patients. Early retrograde flow of gastric contents into the esophagus is possible because the hernia acts as a reservoir. Furthermore, because of its altered positioning, the active contractions of the diaphragm, which normally enhance LES pressure during inspiration, may not be as effective. Many patients with a hiatal hernia have GERD and, most likely, a compromised LES.

The role of pepsin in the etiology of GERD is unclear and probably underestimated, since increased concentrations of pepsin at low pH can induce esophageal injury, whereas they would be harmless to the mucosa at neutral pH. Furthermore, the same concentrations of pepsin that can be injurious in patients with GERD do not cause harm in healthy controls.

Once reflux occurs, the presence and extent of mucosal damage depend on the efficacy of other gastroesophageal defensive factors. Not all patients who experience reflux develop esophagitis. Esophagitis occurs in those with reduced esophageal clearance or impaired mucosal resistance. Reduced esophageal clearance results in an increased duration of exposure to gastric contents, while decreased mucosal resistance predisposes the mucosa to injury.

In contrast to the gastric epithelium, the esophageal epithelium is much less resistant to the damaging effects of acidic gastric contents and, therefore, potentially at greater risk for injury following acid exposure. Moreover, the esophageal epithelium does not share the capacity for rapid repair or the ability to create a protective mucoid cap.

A recent study demonstrated that cultured esophageal cell restitution and proliferation were inhibited in a graduated manner with decreasing pH and increasing time of acid exposure. The mucosal repair was completely and irreversibly abolished when the mucosa was exposed to a pH of less than 3.0.

To prevent mucosal injury and effectively ensure healing of esophagitis, the treatment of patients with GERD depends on the ability to increase and maintain gastric pH above 4.0. This finding was confirmed in a meta-analysis of clinical trials of patients with GERD and esophagitis and clinical pharmacodynamic studies with the same dose regimen.

**PATHOPHYSIOLOGY OF GERD SYMPTOMS AND MUCOSAL INJURY**

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ments of antisecretory drugs. Drug therapy that raised intragastric pH and intraesophageal pH above 4.0 achieved the best clinical results. A strong correlation (P < .05; r = 0.87) was found between the esophagitis healing rate at 8 weeks and the duration, in hours, that intragastric pH was maintained above 4.0.19 Furthermore, another more recent meta-analysis24 has confirmed that the speed of symptom relief and healing in patients with grade II through IV esophagitis is directly related to the degree of acid suppression.

**DRUG CLASSES THAT RAISE GASTRIC pH**

In the treatment of GERD, antacids, H2RAs, and PPIs all raise intragastric pH—albeit to different degrees—for differing durations and through different mechanisms of action. Other agents used to treat GERD include the prokinetic agents cisapride and metoclopramide sulfate and the site-protective agent sucralfate, which do not affect pH in any substantial way.

Various antacid preparations neutralize gastric acid within the lumens and raise the pH of refluxed gastric contents, but to varying degrees. Although antacids are used by many to alleviate intermittent, mild GERD-related symptoms, particularly heartburn, they do so for relatively short periods, thereby requiring frequent administrations per day. In addition, antacids do not affect the volume of acid secretion or significantly help heal esophagitis or prevent the complications of GERD.25-27

Given the less-than-ideal effects of antacid preparations, the advent of the H2RAs cimetidine, ranitidine, famotidine, and nizatidine provide some improvement for the treatment of GERD. They decrease gastric acid secretion by reversible, competitive inhibition of histamine-stimulated acid secretion and are considered equivalent in acid suppression when given in equipotent doses.27 However, given the cholinergic and gastrin pathways involved in regulating acid secretion, the H2RAs are not able to control acid secretion reliably throughout a 24-hour period in all patients. Although effective in reducing basal acid secretion, they are much less effective at inhibiting meal-stimulated acid secretion.27-29 Thus, H2RAs are relatively ineffective for controlling the symptoms that result from postprandial reflux.

Tolerance may occur with the use of H2RAs and result in an approximate 50% decrease in efficacy that is usually not overcome by increasing the dose.27,30 The clinical impact of this phenomenon was illustrated in a recent study31 in which the dose of ranitidine was increased from 150 mg twice daily to 300 mg twice daily in patients who continued to experience heartburn following 6 weeks of therapy. Fewer than half the patients who received the higher dose reported any further relief of heartburn and less than 20% reported complete symptom relief. No significant differences were noted with regard to the frequency of heartburn (P > .05), heartburn-free days (P = .16), or epigastric pain scores (P < .05). In 1993, Sontag32 published an exhaustive analysis of controlled trials of H2RA treatment in patients with GERD, concluding that only half the patients who received H2RAs for 6 to 12 weeks had relief of reflux symptoms when compared with placebo. Complete mucosal healing was achieved in patients enrolled in just one 12-week placebo-controlled study of famotidine (50% vs 26% of the famotidine and placebo-controlled groups, respectively; P < .05). In uncontrolled studies, the healing rates were as high as 70% after 12 weeks of treatment.

The introduction of the PPIs omeprazole, lansoprazole, and pantoprazole has provided, for the first time, effective medical treatment for patients with GERD. They reduce gastric acid secretion by inhibiting activity of the gastric hydrogen/potassium adenosine triphosphatase (H+/K+-ATPase). These agents are also protonated in the acidic gastric environment to active forms, which irreversibly bind to sulphydryl groups on the H+/K+-ATPase molecule, rendering it inactive.

In contrast to the H2RAs, the activity of the PPIs results in profound, long-lasting acid suppression, which recovers only when therapy is discontinued and the newly synthesized H+/K+-ATPase from parietal cells is not blocked. Also, unlike the H2RAs, the PPI agents block the final step of acid secretion and inhibit acid secretion regardless of the stimulus. Omeprazole, 20 mg, has a low initial bioavailability (35%), although this increases to 60% with repeated administration.33 Lansoprazole and pantoprazole have higher bioavailability, averaging 80% to 90% and 77%, respectively.34,35 The individual PPIs also differ regarding their onset of action and duration of effect, as measured by maximum serum concentrations and elimination half-life, respectively. Omeprazole reaches maximum plasma concentrations between 1.0 and 6.0 hours,36 while lansoprazole peaks at 1.3 to 2.9 hours37 and pantoprazole at 2.8 hours.38 The elimination half-lives for the 3 agents are 0.6 to 1.0 hour for omeprazole,37 1.3 to 2.9 hours for lansoprazole,34 and 0.9 to 1.9 hours for pantoprazole.38 These differences may help explain the differences seen in the pharmacodynamic effects of these agents.

**REVIEW OF SELECTED INTRAGASTRIC pH STUDIES**

Numerous placebo-controlled and comparative studies have been performed that evaluate the effect of H2RAs and PPIs on intragastric pH. While different methods of assessing intragastric pH have been used that make direct comparisons difficult, definitive trends are clear.

Although the H2RAs effectively raise intragastric pH, standard doses are ineffective in a substantial proportion of patients with GERD. Patients with reflux disease often require higher double-dose regimens to attain an intragastric pH above the critical threshold of 4.0. Bell and Hunt39 analyzed intragastric pH data for various dose regimens of H2RAs and for several omeprazole dose regimens. Figure 1 illustrates that H2RAs cannot maintain pH greater than 4.0 for more than about 9 hours at best with ranitidine, 300 mg given at bedtime, and less than 4 hours at worst with cimetidine, 400 mg given 4 times daily. More recent data support these findings.40-47

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The PPIs are significantly more effective at attaining and maintaining an intragastric pH above 4.0 compared with the H2RAs. A meta-analysis of GERD clinical trials and pharmacodynamic pH studies published in 1992 by Bell et al19 found that PPI therapy maintained intragastric pH above 4.0 for between 15 and 21 hours daily compared with approximately 8 hours daily with the H2RAs (Figure 2). More recent comparative studies show similar results50-52 and have been confirmed by meta-analysis by Chiba et al.24

The acid-inhibitory effects of the PPIs omeprazole and lansoprazole are determined by their dose, extent and consistency of their bioavailability, and plasma half-life.50 In the treatment of patients with acid-related diseases, omeprazole is used at a recommended daily dose of 20 mg and lansoprazole is used at a recommended daily dose of 30 mg. While the bioavailability of omeprazole is only 35% after the first dose, the bioavailability of lansoprazole is greater than 85% following the first dose and remains constant after repeated administrations.50-52 The bioavailability of omeprazole increases to approximately 60% with repeated administrations.50,52

Given its increased bioavailability, lansoprazole would be expected to attain maximal acid-inhibitory effects sooner than omeprazole. One study53 that evaluated the time to maximum inhibition of gastric acidity following repeated oral administration of lansoprazole, 30 mg, found a rapid onset of action. Lansoprazole, 30 mg, increased the mean 24-hour intragastric pH significantly from baseline on day 1 (from a baseline pH of 2.11 to 3.57; P < .05). The maximum effect occurred as early as 6 hours following administration of the first dose. In a recently published study,50 10 healthy male volunteers were treated for 5 consecutive days with a single morning dose.
of lansoprazole, 15 mg; lansoprazole, 30 mg; omeprazole, 20 mg; omeprazole, 40 mg; and placebo. At day 1, meal-stimulated acid secretion was decreased by 45% following administration of 30 mg of lansoprazole and by 16% and 42% following omeprazole, 20 mg and 40 mg, respectively. Following 5 days of therapy, the reduction in meal-stimulated acid secretion was 82% with lansoprazole, 30 mg, compared with 39% with omeprazole, 20 mg. After 5 days of therapy, the reduction in meal-stimulated acid secretion was 83% with omeprazole, 40 mg. The investigators reasoned that the decreased effects observed with omeprazole may be due to its low first-day bioavailability and that the antisecretory effects of lansoprazole, 30 mg, equaled those of omeprazole, 40 mg. Given the results of this study, 30 mg of lansoprazole is likely to display greater gastric acid antisecretory efficacy than 20 mg of omeprazole and, therefore, may prove advantageous in the treatment of acid-related diseases when these doses are used.

Several controlled, double-blind pharmacodynamic studies in healthy volunteers have shown that lansoprazole, 30 mg, sustains the 24-hour intragastric pH above 3.0 for a longer duration than omeprazole, 20 mg. Intragastric pH measurements after lansoprazole, 30 mg once daily, and omeprazole, 20 mg once daily, administration were compared in a crossover study of 12 healthy volunteers. The 2 treatments were similar with regard to their effect on 24-hour intragastric pH, daytime pH, nighttime pH, and total time that pH was greater than 4.0. While the effect of lansoprazole, 30 mg, on gastric pH was always greater than that of omeprazole, 20 mg, the difference between the 2 agents reached statistical significance only for the percentage of time lansoprazole sustained pH greater than 3.0 during the 24-hour period (P < .05).

In a 3-way crossover study of 14 healthy male volunteers given 15 mg and 30 mg of lansoprazole and 20 mg of omeprazole once daily, the mean intragastric 24-hour pH was significantly greater with lansoprazole, 30 mg (pH = 4.91), than either lansoprazole, 15 mg (pH = 4.03), or omeprazole, 20 mg (pH = 4.16) (P < .05). The mean percentage of time that intragastric pH was above 3.0, 4.0, and 5.0 (70%, 65%, and 55% of the 24-hour period, respectively) was significantly greater with lansoprazole, 30 mg, than with the other 2 regimens (P < .01).

In a crossover comparison of the effect that low-dose PPI therapy has on gastric acidity, 12 healthy _H pylori_-negative males were treated with lansoprazole, 15 mg; omeprazole, 10 mg; and omeprazole, 20 mg, for 5 days. Treatment with lansoprazole, 15 mg; omeprazole, 10 mg; and omeprazole, 20 mg, significantly increased the percentage of time the median 24-hour intragastric pH was greater than 4.0 compared with the control period (30%, 25%, 36%, and 8%, respectively; P = .002). Comparisons between lansoprazole and omeprazole and between both doses of omeprazole revealed no significant difference in median intragastric pH and the time over pH 4.0.

Blum et al recently compared 2-dose regimens of lansoprazole to omeprazole and to ranitidine at the recommended dose for the treatment of erosive esophagitis. This was a randomized, double-blind, 4-way crossover study in 29 healthy male volunteers comparing the effects on intragastric pH of lansoprazole, 15 mg once daily, lansoprazole, 30 mg once daily, omeprazole, 20 mg once daily, and ranitidine, 150 mg 4 times daily. Ambulatory 24-hour pH was monitored at baseline and on the last day (day 5) of each crossover period, and mean intragastric pH and proportion of time pH was greater than 3.0, 4.0, 5.0, and 6.0 were calculated. Lansoprazole, 30 mg, showed a significantly higher (P ≤ .05) mean intragastric pH (pH = 4.53) when compared with lansoprazole, 15 mg (pH = 3.97), omeprazole (pH = 4.02), and ranitidine (pH = 3.59). Lansoprazole, 30 mg, also achieved a significantly longer duration with intragastric pH (P ≤ .05) above 3.0 and 4.0 during the 24-hour period compared with the other treatments (Figure 3).

The results obtained in this study are similar to a prior investigation that compared the acid inhibitory activity of omeprazole, lansoprazole, and famotidine. Ten healthy volunteers were treated sequentially with lansoprazole, 30 mg once daily in the morning; famotidine, 20 mg twice daily; and omeprazole, 20 mg once daily in the morning. Lansoprazole, 30 mg, achieved a significantly (P < .05) longer time with 24-hour intragastric pH greater than 4.0 compared with famotidine (Figure 4). Although the 24-hour profile of acid suppression with the 2 PPIs was similar, the percentage of time that intragastric pH was above 4.0 in different periods with lansoprazole was greater than with omeprazole at any time of the day. This difference in acid-inhibitory ef-
fect was significant (P < .05) at periods 0 to 12 and 18 to 24.

The relative antisecretory efficacy of pantoprazole, the newest of the PPIs, appears to be comparable to that of omeprazole yet less effective than lansoprazole in 2 studies. Intragastric pH measurements were compared after pantoprazole and omeprazole (40 mg once daily for each agent) administration in a crossover study with 12 healthy volunteers. No differences were found between the 2 agents regarding their effect on 24-hour intragastric pH, daytime pH, nighttime pH, or duration that pH was greater than 4.0.

Twelve healthy volunteers participated in a 2-way crossover study comparing intragastric pH after lansoprazole, 30 mg; and pantoprazole, 40 mg. Lansoprazole maintained pH above 4.0 significantly longer than pantoprazole (P = .03 and P = .02, respectively) on days 1 and day 7 and during the daytime hours (P = .004 and P = .001 on days 1 and 7, respectively).

In summary, the results of several meta-analyses and several recent direct comparison studies confirm that the PPIs are more effective at achieving and maintaining intragastric pH above 4.0 when compared with standard or high-dose H2RAs. Furthermore, data suggest that lansoprazole, 30 mg, is significantly more effective at raising intragastric pH above 4.0 and sustaining this effect for longer than omeprazole, 20 mg; or pantoprazole, 40 mg daily. Moreover, lansoprazole, 30 mg, appears to be equipotent to omeprazole, 40 mg, in inhibiting meal-stimulated gastric acid secretion.

Results of a recent study suggest that lansoprazole, 15 mg, is comparable to omeprazole, 10 mg and 20 mg, for raising intragastric pH, with no difference noted between the 2 doses of omeprazole.

**CLINICAL EFFECTS OF GASTRIC pH CONTROL**

The effective and sustained increase in intragastric pH manifested by the PPIs translates into significantly more rapid relief of symptoms and greater healing compared with the H2RAs. The healing of GERD achieved after 2 to 4 weeks with a once-daily dose of a PPI is greater than that achieved after 12 weeks with 2- to 4-times-daily doses of an H2RA. In refractory GERD, the H2RAs are ineffective, whereas the PPIs are invariably effective in controlling symptoms and healing erosive esophagitis.

Numerous comparative studies have found that once-daily PPI therapy can achieve healing rates of greater than 90% in grade II through IV esophagitis compared with approximately 60% with H2RA therapy 2 to 4 times daily when each class of drug is given for 8 weeks. A recent comprehensive meta-analysis of published GERD trials by Chiba et al evaluated 43 controlled trials performed in 7635 patients with erosive GERD (grade II through IV esophagitis). Of all drug classes studied in the various trials, the PPIs administered once daily consistently demonstrated the highest healing rates (mean ± SD, 83.6% ± 11.4%; 95% confidence interval, 79.1-88.1), irrespective of drug dose or duration of treatment (Figure 5). In contrast, the overall rate of esophagitis healing in patients treated with high-dose H2RA given up to 4 times daily for 12 weeks or longer was 51.9% ± 17.17% (mean ± SD). Moreover, speed of healing with PPI treatment was calculated to be approximately twice as fast as that observed with the H2RAs (11.7% vs 5.9% of patients healed per week, respectively).

Most important, PPI therapy is associated with a more rapid relief of heartburn than is H2RA therapy. In the meta-analysis by Chiba and colleagues, 11.5% of PPI-treated patients per week reported relief of their heartburn compared with 6.4% of H2RA-treated patients. In general, the mean heartburn-free proportion of patients was 77% in those treated with PPIs compared with 48% of those treated with H2RA. In a study of patients with erosive esophagitis comparing lansoprazole, 30 mg once daily, lansoprazole, 60 mg once daily, and ranitidine, 150 mg twice daily, for 8 weeks.
where healing rates were 92%, 91%, and 53%, respectively, symptom relief at 4 weeks was achieved in 72%, 77%, and 39%, respectively.

Similar to the results observed in comparative trials with lansoprazole and H2RAs, pantoprazole is also more effective than the H2RAs for healing erosions and relieving symptoms. Following 8 weeks of treatment, 82% of patients treated with pantoprazole, 40 mg once daily, were healed compared with 67% (P < .05) of patients treated with ranitidine, 150 mg twice daily. Compared with ranitidine, at 4 weeks, symptomatic relief of heartburn, acid regurgitation, and odynophagia was reported in 72% vs 52% (P < .05) in the pantoprazole and ranitidine groups, respectively. Similarly, in an 8-week study, pantoprazole, 40 mg once daily, healed 93% of patients compared with 72% of patients (P < .001) treated with lamotidine, 40 mg once daily.

The PPIs are effective in healing all grades of erosive esophagitis, including H2RA refractory cases. Five controlled trials have confirmed that treatment with either omeprazole or lansoprazole in patients refractory to H2RA therapy markedly increased esophagitis healing. In comparative studies performed with omeprazole, significantly (P < .05) higher rates of healing were observed at weeks 4, 8, and 12, despite the use of high-dose ranitidine (300 mg twice daily). By week 12, 90% to 97% of patients treated with omeprazole, 40 mg once daily, were healed compared with 47% to 64% of those treated with ranitidine, 300 mg twice daily. Similarly, lansoprazole produced significantly higher healing rates at 4 and 8 weeks compared with ranitidine in patients resistant to H2RAs. By week 8, 83% to 89% of patients treated with lansoprazole, 30 mg once daily, were healed compared with 35% to 38% of those treated with ranitidine, 150 mg twice daily.

In addition to healing erosive esophagitis effectively, maintenance therapy with a PPI once daily prevents recurrence of erosive lesions. Studies confirm that up to 89% of patients taking standard doses of a PPI as long-term maintenance therapy remain healed, compared with 10% to 25% of patients treated with conventional doses of an H2RA.

While all the PPIs are effective for healing esophagitis, a more rapid relief of symptoms is seen with lansoprazole than with omeprazole, thereby enhancing patients’ wellbeing. In studies comparing lansoprazole and omeprazole in patients with GERD, lansoprazole provided more effective and rapid symptom relief. In a study of 229 patients at 9 Scandinavian hospitals, patients receiving lansoprazole, 30 mg once daily, experienced a significantly (P = .03) greater improvement in heartburn after 4 weeks compared with those receiving omeprazole. Furthermore, the median percentage of days on which patients required antacids during the first 4 weeks was lower in those receiving lansoprazole compared with those receiving omeprazole (11% vs 20%), although this difference was not statistically significant (P = .21). Similar findings were reported by Mee and colleagues, who studied 282 patients with GERD treated with lansoprazole, 30 mg once daily, and 283 patients treated with omeprazole, 20 mg once daily. At day 3 of treatment, a significant improvement in daytime symptoms of heartburn was reported by patients in the lansoprazole group compared with the omeprazole group (P = .05). In addition, at day 7, a significant (P = .03) improvement in daytime epigastric pain was reported by the lansoprazole group compared with those taking omeprazole. The findings of these 2 studies were further confirmed in a large US study of 1284 patients with endoscopically diagnosed erosive reflux esophagitis who were randomized to receive lansoprazole, 15 mg (n = 218), lansoprazole, 30 mg (n = 422), omeprazole, 20 mg (n = 431), or placebo (n = 213) once daily for 8 weeks. Patients receiving lansoprazole, 30 mg, experienced significantly less day and night heartburn than did patients receiving omeprazole, 20 mg, after the first day of therapy (P < .05). In addition, during the first week of treatment, those taking lansoprazole, 30 mg, experienced significantly less night and day heartburn compared with those taking omeprazole (P < .05). During all 8 weeks of therapy, patients treated with omeprazole experienced a significantly higher percentage of nights with heartburn compared with those treated with lansoprazole, 30 mg.

A recently presented meta-analysis of 37 double-blind, randomized, comparative studies involving 77 treatment arms and 8951 patients with erosive esophagitis confirmed the findings of earlier investigators. The H2RAs were not effective, even at higher doses in healing erosive esophagitis. Omeprazole, lansoprazole, and pantoprazole were all significantly (P < .05) more effective at healing erosive esophagitis lesions compared with the H2RAs, even in patients with lesions refractory to H2RA treatment. Although there were no significant differences between PPIs in the healing of erosive esophagitis, lansoprazole relieved significantly more symptoms than did omeprazole during the first 2 weeks of treatment.

COMMENT

Reflux of acidic gastric contents into the esophagus is common and, in most individuals, this occurs relatively infrequently and produces no harm. However, in others erosive esophagitis may develop with associated symptoms and the potential for complications. Once the esophageal epithelium is damaged, reepithelialization is prolonged, even under ideal conditions of normalizing intraesophageal acid exposure.

It seems intuitive that the key to preventing further mucosal injury and allowing the injured mucosa to repair itself is to eliminate the injurious acidic reflux. Furthermore, evidence from pathophysiologic and clinical studies indicates that, to protect the damaged esophageal mucosa from further damage and facilitate healing, therapy must attain a “critical pH threshold” for intragastric pH of greater than 4.0 for 20 to 22 hours of the 24-hour day. Before the advent of the PPIs these goals were not attainable.

The superiority of the PPIs in controlling 24-hour intragastric pH is undisputed, and numerous stud-
ies confirm that, compared with the H$_2$RAs, omeprazole, lansoprazole, and pantoprazole are all more effective in attaining a higher intragastric pH and sustaining pH greater than 4.0 for a longer duration. This leads to significantly higher healing rates and to more rapid healing and symptom relief. While all 3 PPIs are clinically effective, results of clinical studies suggest that lansoprazole, 30 mg, may be more effective compared with omeprazole, 20 mg, and pantoprazole, 40 mg, at achieving and maintaining a pH threshold of 4.0 or greater and is more effective at producing a faster onset of symptom relief. Results of a recent meta-analysis$^{75}$ confirm that lansoprazole relieved significantly more erosive esophagitis-related symptoms compared with omeprazole during the first 2 weeks of treatment.

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Reprints: Richard H. Hunt, MD, FRCP, Division of Gastroenterology, McMaster University Medical Centre, 1200 Main St W, Room 4W8, Hamilton, Ontario L8N3Z5, Canada.

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