



Profile and assessment of GERD pharmacotherapy

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■ ABSTRACT

The choice of a medical therapy to treat gastroesophageal reflux disease (GERD) centers around several factors, including the efficacy and safety of the agent and the severity of the patient's symptoms and complications. Although the efficacy of antacids and alginic acid has not been proven definitively in clinical trials, these agents are effective against mild GERD symptoms in clinical practice. Along with sucralfate, these agents are also useful in special populations, such as pregnant women, for whom acid-suppressive therapy may not be the best option. The withdrawal of cisapride from the US market has lessened the role of promotility agents for treating GERD, as their efficacy must be weighed against their side effects. Acid-suppressive agents have become the drugs of choice for GERD. Both proton pump inhibitors (PPIs) and histamine H₂-receptor antagonists effectively and safely treat GERD. However, PPIs have been shown to provide the highest levels of GERD symptom relief and esophageal healing to the most patients, in the shortest time, and with the fewest side effects.

Pharmacotherapy is considered first-line treatment for patients with gastroesophageal reflux disease (GERD). Although some guidelines recommend instituting lifestyle changes at the same time as an initial trial of empiric medical therapy,¹ others note that these diet and lifestyle changes have little therapeutic benefit, and recommend medical therapy as initial treatment.² The following medical therapies are available for

the treatment of GERD:

- **Prokinetic agents**, which target the underlying motility dysfunction that causes GERD
- **Mucosal-protective agents**—ie, sucralfate, which binds with damaged mucosa to form a barrier against harmful acid reflux, and alginic acid, which forms a foamy barrier on top of the refluxate to protect the esophagus
- **Acid neutralizers (antacids)**, which work locally to raise the pH of the refluxate
- **Acid-suppressive agents**—ie, histamine H₂-receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs), which inhibit acid production in the parietal cell.

Guidelines also differ on which medical therapy should be used as initial GERD treatment. Therapy for any disease must be effective and safe, and fit the needs of the patient. Other issues, such as concomitant conditions, recurrence of symptoms, and cost to treat, should also be considered when deciding on a course of therapy.

This article examines the safety and efficacy of the available medical therapies for GERD. End points for the efficacy of these agents include:

- Symptom relief, which is a measure of the reduction in symptoms (usually heartburn and regurgitation, but some studies assess noncardiac chest pain and other atypical or extraesophageal symptoms)
- Symptom resolution, which indicates the absence of symptoms
- Erosive esophagitis healing rates.

Maintenance studies have examined maintenance of erosive esophagitis healing and symptom recurrence. Safety considerations include adverse events and the effects of long-term treatment.

This article also presents data from placebo-controlled and comparative trials of the available H₂RAs and the available PPIs, as well as trials comparing efficacy between H₂RAs and PPIs. Much of the literature on GERD pharmacotherapy focuses on the safety and comparative efficacy of these acid-sup-

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pressive agents. PPIs have been recognized as the most effective medical therapy for GERD symptom relief, for healing all grades of erosive esophagitis, and for maintenance of healing. Although some patients experience symptom relief and healing of erosive esophagitis with H₂RAs, PPIs produce more frequent and rapid symptom relief and esophageal healing for a greater percentage of patients.¹

■ PROKINETIC AGENTS

Prokinetic agents that treat GERD increase lower esophageal sphincter pressure (LES), accelerate gastric clearance, stimulate esophageal peristalsis, increase the amplitude of esophageal contractions, or perform a combination of two of these actions.

All prokinetic agents (bethanechol, metoclopramide, domperidone, and cisapride) are effective, to varying degrees, in improving GERD symptoms and healing esophagitis. However, efficacy data for these agents come from small, sometimes poorly designed studies, often without a placebo control. Also, the adverse-event profile of these agents must be weighed against any clinical benefit of GERD treatment. Although domperidone (available in Canada but not in the United States) is well tolerated, metoclopramide and bethanechol have been associated with significant adverse events (**Table 1**).³ Cisapride, in particular, although the most effective of the prokinetic agents for treating GERD, was removed from the US market because of deaths associated with cardiac arrhythmia.

Bethanechol

Bethanechol is a direct-acting muscarinic receptor agent that acts by stimulating the parasympathetic nervous system to release acetylcholine. It has been shown to increase LES and improve esophageal peristaltic clearing.

Clinical efficacy. Some small, double-blind, placebo-controlled studies have investigated the efficacy of bethanechol in GERD treatment, with mixed results. One placebo-controlled study conducted in 20 patients found that a 2-month course of bethanechol 25 mg four times daily reduced heartburn and reduced antacid use.³ However, in another study of 44 patients by Thanik and colleagues,⁴ the improvement of GERD symptoms in patients receiving bethanechol plus antacids was not statistically significantly different from that in patients receiving antacids plus placebo.

Results also differ among studies examining the

efficacy of bethanechol in healing erosive esophagitis. In a comparative trial of bethanechol and cimetidine, the two agents had fairly similar healing rates (52% of patients receiving bethanechol and 68% of those receiving cimetidine experienced complete healing). Both agents were administered with high doses of antacids, which may have helped produce these high healing rates.³ Interestingly, although Thanik and colleagues⁴ found bethanechol to be no more effective than placebo in improving GERD symptoms, 45.5% of patients receiving bethanechol 25 mg four times daily experienced complete healing of erosive esophagitis, compared with 13.6% of patients receiving placebo plus antacids ($P < 0.015$).

Safety. Unfortunately, at the dosage level necessary to treat GERD (25 mg four times daily), bethanechol can cause significant side effects, such as abdominal cramping, blurred vision, fatigue, and increased urinary frequency. Side effects occur in about 10% to 15% of patients, and are more common in the elderly. Bethanechol is also associated with a long list of contraindications (**Table 1**) that compromise its use as an anti-GERD agent.³

Metoclopramide

Metoclopramide is a dopamine antagonist. Although its precise mechanism of action is unclear, it seems to sensitize tissues to the action of acetylcholine. It has been shown to increase the amplitude of gastric and esophageal contractions, increase LES, and increase the speed of gastric emptying and intestinal transit.

Clinical efficacy. In two small, placebo-controlled studies in which 31 and 15 patients with GERD received metoclopramide 10 mg three times daily, symptom improvement did not differ significantly between the treatment and control groups. However, in studies conducted in 30 and 31 patients with GERD, a higher dosage of the agent, 10 mg four times daily, either alone or in combination with an antacid, was more effective than placebo at improving symptoms.^{5,6}

Comparative studies have found that metoclopramide is as effective as H₂RAs (cimetidine and ranitidine) in relieving heartburn and other GERD symptoms.^{7,8} All of these comparative trials were conducted in small patient populations,³ and all but one were conducted without a placebo control.⁸ The largest one, conducted in 73 patients, found no difference in symptom relief between patients given cimetidine 400 mg four times daily alone and those

TABLE 1

Contraindications and adverse events associated with prokinetic agents³

Agent	Contraindications	Adverse events
Bethanechol	- Intravenous or intramuscular use may cause severe cholinergic reaction - Hyperthyroidism, peptic ulcer, bronchial asthma, mechanical obstruction of gastrointestinal or lower urinary tract, peritonitis, parkinsonism, bradycardia, atrioventricular conduction defects, hypotension, and coronary artery disease	Abdominal cramping, blurred vision, fatigue, and increased urinary frequency in 10% to 15% of patients
Metoclopramide	—	- Antidopaminergic side effects in up to 30% of patients, including drowsiness, lassitude, anxiety, agitation, and motor restlessness - Dystonic reactions in 1% of patients - Parkinson symptoms (tremor, rigidity, akinesia, tardive dyskinesia) rare except with high doses (30–80 mg) - Gynecomastia, galactorrhea, and menstrual disorders
Domperidone	—	- Hyperprolactinemia, resulting in breast enlargement, nipple tenderness, galactorrhea, and amenorrhea, in 10% to 15% of patients - Otherwise well tolerated
Cisapride	—	Deaths associated with cardiac arrhythmia led to voluntary removal from US market

given a combination of cimetidine with metoclopramide 10 mg three times daily.⁹

Although symptom improvement has been demonstrated with metoclopramide, this agent does not seem to be significantly more effective than placebo at promoting healing of erosive esophagitis.³ In the one placebo-controlled study comparing it with cimetidine, metoclopramide improved the appearance of esophageal erosions in 82% of patients, but this was not significantly different from rate with either cimetidine or placebo (78% for each).⁸ In another comparative study, both metoclopramide and ranitidine produced significant healing, but metoclopramide was effective in fewer patients (52% healing rate, vs 81% with ranitidine).¹⁰ The recommended dosage of metoclopramide is 10 mg four times daily, whereas the recommended dosage of ranitidine is 75 mg twice daily.

Safety. To an even greater extent than with bethanechol, side effects are a significant drawback to GERD therapy with metoclopramide. Because it is a centrally acting dopamine antagonist that crosses the blood-brain barrier, antidopaminergic side effects are common, occurring in 20% to 30% of patients. Drowsiness and lassitude are most common, and anxiety, agitation, confusion, hallucina-

tions, and motor restlessness have also been reported.^{3,11} The most serious effects are depression and tardive dyskinesia, which may be irreversible. Adverse events are most common at higher doses and in children, young adults, and the elderly. Other less common adverse events are listed in **Table 1**.

Domperidone

Domperidone is another dopamine antagonist, although it is not available in the United States. It stimulates esophageal peristalsis, increases LES, and accelerates gastric emptying.

Clinical efficacy. As with bethanechol and metoclopramide, data on the efficacy of domperidone in GERD treatment come from small studies. The largest one, conducted in 45 patients, compared domperidone and ranitidine without a placebo control.

The efficacy of domperidone in GERD treatment has not been persuasively proven in well-controlled double-blind studies, and results with domperidone at dosages of 20 mg three or four times daily are inconsistent.³ In one study, domperidone was no more effective than placebo in reducing the number of reflux episodes or improving GERD symptoms, although antacids were used less frequently at the

TABLE 2
Results of comparative trials of sucralfate
in the healing of erosive esophagitis

Investigators	N	Weeks	Patients with healed erosive esophagitis	
			Sucralfate	Comparator
Simon et al ²⁰	41	8	64%	68% (ranitidine)
Hameeteman et al ²¹	42	8	31%	14% (cimetidine)
Laitinen et al ²²	68	6	53%	34% (alginate + antacid)

end of the trial compared with baseline in the domperidone group.¹² Other studies have shown domperidone to be effective in relieving symptoms but not in healing esophagitis.³ In two non-placebo-controlled comparative trials of domperidone and H₂RAs (ranitidine or famotidine), the two agents proved to be similarly effective in symptom relief and in promotion of esophageal healing. However, the combination of domperidone with an H₂RA was not significantly better than each agent given alone.^{13,14}

Safety. Although domperidone is a dopamine antagonist, it does not cross the blood-brain barrier (unlike metoclopramide) and was developed to act as a specific antagonist to the inhibitory effects of dopamine on the gastrointestinal tract. It is well tolerated, with few significant side effects. The adverse events that do occur are related to the stimulation of prolactin release (Table 1) and are seen in approximately 10% to 15% of patients. These events can be seen with metoclopramide use but are more common with domperidone because it is administered in higher doses. Domperidone rarely causes extrapyramidal side effects.³

Cisapride

Any discussion of cisapride must be prefaced with a note on its profile and current market availability. High blood concentrations of cisapride can cause QT prolongation and cardiac arrhythmia, including ventricular arrhythmia, such as torsades de pointes. Coadministration of a number of drugs can reduce hepatic metabolism of cisapride and increase the likelihood of toxic concentrations.

Cisapride was removed from the US market in July 2000 after 341 cases of arrhythmia and 80 deaths were spontaneously reported to the FDA from July 1993 to May 1998. The agent is now available only on a restricted basis through a limited-access program for patients who have failed to respond to or cannot receive alternate therapies.¹⁵

Cisapride acts locally on the gastrointestinal tract and seems to facilitate release of acetylcholine from postganglionic neurons in the myenteric plexus. There is also evidence that it influences the activity of other chemical mediators of mucosal and muscular function in the gut, interacting with the serotonin 5-HT₄ receptor in the myenteric plexus. Cisapride increases smooth muscle contractility, increases LESP, and enhances esophageal peristaltic function.

Clinical efficacy. Before its removal from the US market, cisapride was indicated for supplemental treatment of nocturnal heartburn symptoms. It was the most effective pro motility agent available for the treatment of GERD, in terms of both higher efficacy and fewer reported side effects. In clinical trials, cisapride was consistently better than placebo at improving the symptoms of GERD and promoting healing of erosive esophagitis. Optimal efficacy for relieving symptoms was achieved at a dosage of 10 mg three times daily, whereas 10 mg four times daily showed efficacy in healing esophagitis. One study found that 10 mg of cisapride given four times daily was as effective as 20 mg given four times daily in healing esophagitis.¹⁶

Comparative trials of cisapride and H₂RAs yielded similar efficacy rates in healing esophagitis.³ Gal-miche and colleagues¹⁷ found that cimetidine 400 mg and cisapride 10 mg, each given four times daily, produced endoscopic healing rates of 57% and 56%, respectively, in patients with erosive esophagitis grades I to III (ie, mild to moderate esophagitis). (Here and except where noted otherwise, references to erosive esophagitis grades in this article are to the Savary-Miller classification system.)

MUCOSAL-PROTECTIVE AGENTS

Sucralfate

Sucralfate is a mucosal-protective agent that binds to inflamed tissue, creating a protective barrier. It blocks diffusion of gastric acid and pepsin across the barrier and inhibits the erosive action of pepsin and bile.¹⁸

Sucralfate is available in the United States in

tablets and in suspension form. As suspension, sucralfate is administered in 1-g doses four times daily. Physicians rarely prescribe this agent to treat GERD, but it can be useful as an anti-GERD therapy in special populations, such as in women who are pregnant. Although sucralfate contains aluminum, which can be harmful to a fetus, little systemic absorption of the agent occurs. As a result, sucralfate is considered safe enough for the treatment of heartburn in pregnant women.¹⁹

Clinical efficacy. The findings of three comparative, non-placebo-controlled studies^{20–22} examining the effects of sucralfate in patients with all grades of erosive esophagitis are summarized in **Table 2**. The trials compared sucralfate with H₂RAs or with alginic acid plus antacids. Patients in all three studies had endoscopically confirmed reflux esophagitis, and the results of therapy were endoscopically confirmed as well. The degree of healing with sucralfate correlated with the degree of injury, with higher grades of erosive esophagitis responding less favorably to treatment. In all three trials, symptom improvement was rated as equally good for patients in all groups. Esophagitis healing rates among the sucralfate and H₂RA recipients were not statistically significantly different in one trial²⁰ but did differ in another study,²¹ with more patients showing healed or improved esophagitis in the sucralfate group. In the remaining study,²² sucralfate generated complete healing more often than did alginic acid/antacid. However, these studies are significantly limited by their relatively small size (40 to 70 patients) and lack of a placebo control.

Other studies have been conducted in more specific patient populations and have included a placebo arm as a comparison. Chiba and colleagues²³ pooled data from several studies of the erosive esophagitis healing rates achieved with various agents, including sucralfate, in patients with grades II through IV esophagitis (**Figure 1**). Healing occurred in an average of 39% of patients who received sucralfate, but this healing rate was accompanied by a very large 95% confidence interval (3.6% to 74.8%), indicating that it was not statistically significantly different from the rate with placebo.

Sucralfate has also been studied in patients with GERD without erosive esophagitis. Simon and colleagues²⁴ tested the effects of sucralfate gel and placebo in 141 patients with moderate to severe GERD but with no esophageal erosions or ulcers. The overall response rate after 6 weeks of treatment was 71%

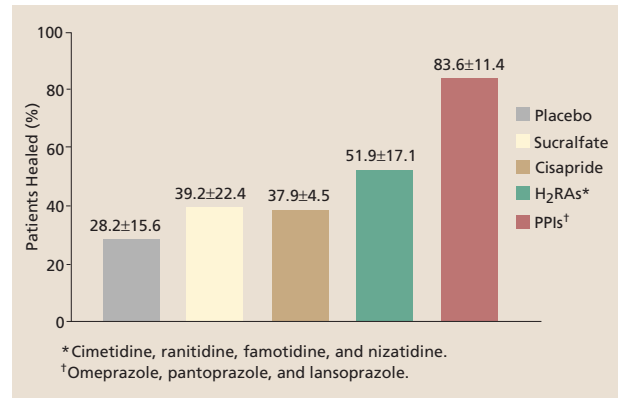


FIGURE 1. Overall pooled healing rates for placebo, sucralfate, cisapride, H₂RAs, and PPIs in patients with Savary-Miller grades II to IV erosive esophagitis.²³

with sucralfate, compared with 29% with placebo ($P < 0.0001$). Improvement in the maximum severity of daytime and nighttime heartburn occurred in 77% and 67%, respectively, of patients given sucralfate, compared with 48% and 51%, respectively, of patients given placebo.

Alginic acid

Alginic acid is often given in combination with an antacid. The first component provides a floating barrier on the gastric pool to minimize contact between gastric contents and esophageal mucosa, while the antacid temporarily neutralizes stomach acid.²⁵ Like antacids alone, this combination therapy helps to control mild to moderate reflux symptoms in clinical practice.²⁶ Tytgat and Nio¹¹ noted that improvement in GERD symptoms occurred in three of four studies that compared alginate/antacid combination therapy with placebo. However, when compared with antacids alone, the alginate combination therapy was superior in only one of four studies. Convincing proof of esophageal healing has never been obtained in any study, and alginic acid therapy is probably no better than antacid therapy in treating moderate to severe GERD.²⁶

ANTACIDS

Antacids are the most widely used agents for treating GERD because patients with mild heartburn often self-medicate with these over-the-counter drugs and never seek treatment for their reflux symptoms. Available in liquid and tablet forms, antacids are used as needed. Some patients use antacids to supplement other anti-GERD therapies. In clinical

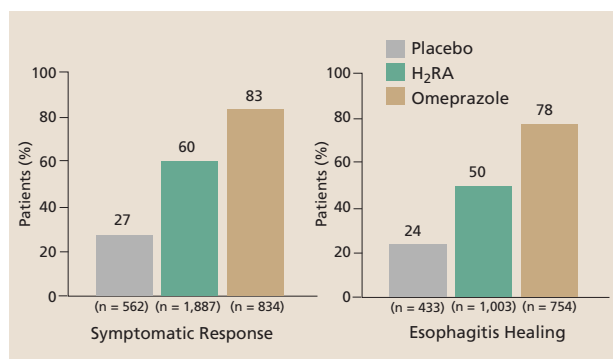


FIGURE 2. Symptom response rates and esophagitis healing rates in patients with GERD receiving H₂RAs, omeprazole, or placebo. The H₂RA dosages represented here are cimetidine 800 to 1,600 mg/day, ranitidine 300 to 600 mg/day, nizatidine 600 mg/day, and famotidine 40 mg/day, all given in divided doses either twice or four times daily. Omeprazole was given at a dosage of 20 mg to 60 mg once daily.¹

practice, antacids help to control mild to moderate reflux symptoms in a large proportion of patients.²⁶ Because they act locally, antacids are considered first-line therapy for pregnant women who experience heartburn. However, magnesium-containing agents should be avoided in the latter part of pregnancy.¹⁹

Clinical efficacy. Despite widespread use of antacids, definitive evidence of their therapeutic benefit in the treatment of GERD is limited by the paucity of well-designed, large, placebo-controlled trials. For the placebo-controlled studies that are available, results are conflicting.

One placebo-controlled study comparing a high-dose antacid (10 mL seven times daily) with an H₂RA in 37 patients with GERD found that symptom improvement was better in the antacid group than in the placebo group, but healing of erosive esophagitis was not. However, another study in 32 patients found that placebo actually performed slightly better than the high-dose antacid (15 mL seven times daily) in relieving GERD symptoms and in healing esophagitis.¹¹

Many studies of the efficacy of antacids in combination with alginic acid have produced favorable results in terms of GERD symptom relief. However, data from these studies, including a non-placebo-controlled comparative trial in children, two open studies without placebo groups, a nonblinded study, and several comparative trials, are of limited use because of the lack of true placebo controls.²⁵

Most studies testing the efficacy of antacids have found that, even at high doses, their effect on healing erosive esophagitis is no better than that of

placebo.^{11,26} For example, in a 4-week, randomized, double-blind, placebo-controlled trial, Furman and colleagues²⁷ compared a high-dose liquid antacid (7 oz/day) given 15 minutes and 1 hour after meals with cimetidine 300 mg four times daily. Patients underwent endoscopy, biopsy, and acid perfusion testing at baseline and at the end of the study. They also were asked to complete symptom diary cards during the study. Only patients given cimetidine had a significant reduction in the frequency and severity of heartburn ($P < 0.05$). The liquid antacid was similar to placebo in its reduction of heartburn severity. No treatment improved regurgitation. Furthermore, neither cimetidine nor the liquid antacid improved any objective measure of GERD severity (endoscopy, acid perfusion test results).

Often in clinical trials, a reduction in the use of antacids is a hallmark of efficacy for other agents (ie, H₂RAs or PPIs).

■ HISTAMINE H₂-RECEPTOR ANTAGONISTS

Histamine H₂-receptor antagonists are acid-suppressive agents that treat GERD by decreasing acid secretion and thus decreasing the causticity of the refluxate. The H₂RAs approved for use in the United States are cimetidine, ranitidine, famotidine, and nizatidine. All are available by prescription and in over-the-counter formulations that are usually one half the standard prescription dose.

Although there are some variations in potency, duration, and onset of action, H₂RAs have similar efficacy rates in symptom relief and healing of esophagitis.¹ Because they are all metabolized via the cytochrome P450 system in the liver, some drug interactions can occur. However, as a class, they are considered very safe, with few side effects.²⁸ In clinical trials, these agents consistently reduced GERD symptoms and promoted esophageal healing at a rate significantly better than placebo, especially in patients with milder grades of esophagitis.

Pharmacokinetic/pharmacodynamic overview

Oral absorption of H₂RAs is fairly rapid, with peak plasma concentrations attained within 1 to 3 hours after administration. A second peak after oral administration has been observed with all H₂RAs except nizatidine. Mean oral bioavailability differs somewhat among the agents, ranging from a low of 40% with famotidine to a high of 80% with cimetidine.

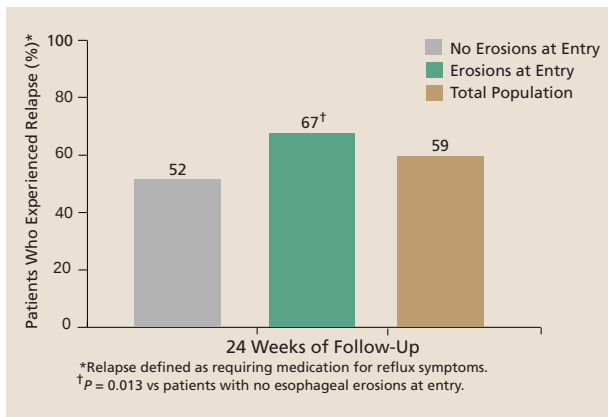


FIGURE 3. GERD symptom relapse rates after discontinuation of a successful 4-week course of treatment with ranitidine 150 mg two or four times daily or placebo.³⁰

Plasma concentrations of H₂RAs and inhibition of gastric acid secretion are directly related, implying a rapid equilibration between drug concentration in plasma and at the site of action.²⁹

In general, the acid-suppressive abilities of H₂RAs are more effective on nocturnal acid secretion. Duration of acid inhibition is longer when the drug is taken in the evening or before bedtime. Equipotent doses of H₂RAs equally inhibit acid secretion.

Efficacy: symptom improvement

Overall, H₂RAs relieve symptoms in 60% of patients with GERD, whereas placebo relieves symptoms in 27% (**Figure 2**).¹ H₂RAs are effective in the control of nocturnal acid reflux episodes as well.¹¹ In patients with no erosive esophagitis and with mild or intermittent GERD symptoms, symptomatic treatment response rates are 70% or higher.²¹ Patients with esophagitis experience lower rates of symptom relief and are more likely to have symptom relapse once therapy is stopped.

Relapse. Hallerback and colleagues³⁰ examined symptom relapse in patients after a 4-week course of either ranitidine or placebo. The study included 423 patients with GERD symptoms, most of whom had mild reflux disease; 67.4% had either a normal-appearing esophagus or erythema only. Another 28.1% had grade I esophagitis, which consists of small, isolated lesions. Only 4.5% of this study population had esophagitis grades II through IV. Patients with more extensive injury were excluded.

Initially, patients were randomized to receive either ranitidine 150 mg twice daily or placebo for 2 weeks. After the initial trial, those who were satis-

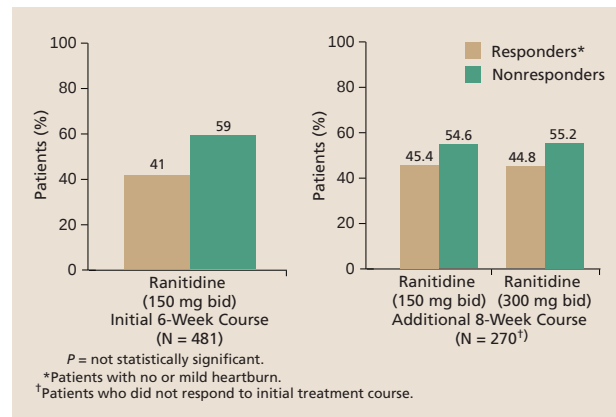


FIGURE 4. Rates of treatment response (heartburn relief) to an initial course of standard-dose ranitidine therapy (150 mg twice daily) and to an additional course of standard-dose or high-dose (300 mg twice daily) ranitidine therapy in patients with GERD.³¹

fied with their treatment (ie, responded to therapy with either improved or complete relief) continued with that therapy. Patients who were not satisfied with their treatment were then re-randomized to receive ranitidine 150 mg two or four times daily for another 2 weeks. Patients whose symptoms did not respond after 4 weeks of therapy were removed from follow-up. After 4 weeks of therapy, all responders were taken off therapy and followed for an additional 24 weeks.³⁰

Figure 3 shows the symptomatic relapse rates in the total population and in patients with and without erosive esophagitis. At 24 weeks of follow-up, symptom relapse had occurred in 52% of patients with GERD who did not have erosive esophagitis compared with 67% of those who did have erosive esophagitis ($P = 0.013$).³⁰

Dosage level. In the Hallerback study,³⁰ the percentage of patients who experienced symptom improvement or complete relief at week 4 was similar in all groups that received ranitidine, regardless of dosage level. This finding was confirmed in a similarly designed study of longer duration. In this study, Kahrilas and colleagues³¹ compared high-dose and standard-dose ranitidine therapy in patients who remained unresponsive after 6 weeks of ranitidine 150 mg twice daily. Of the 481 patients with GERD symptoms who initially received a 6-week course of 150 mg twice daily, 285 (59%) remained symptomatic. Of this group, 270 were re-randomized to receive either 150 mg or 300 mg of ranitidine twice daily. After an additional 8 weeks of therapy, only 44.8% of patients receiving the higher dose of ranitidine and 45.4% of those receiving the lower

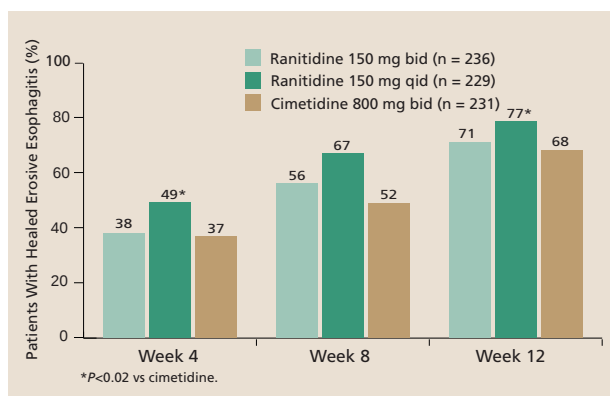


FIGURE 5. Comparison of erosive esophagitis healing rates with ranitidine 150 mg two or four times daily and cimetidine 800 mg twice daily.³²

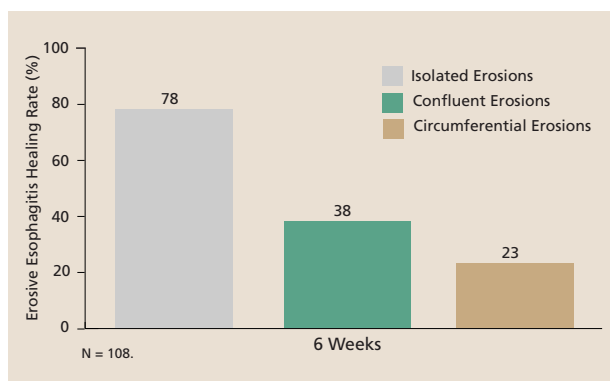


FIGURE 6. Healing of erosive esophagitis with ranitidine 150 mg or 300 mg twice daily, by severity of disease.³³

dose achieved treatment response (mild or no heartburn) (Figure 4).

Efficacy: healing of erosive esophagitis

In general, the results of treatment with H₂RAs are not as good in patients with severe erosive esophagitis. However, healing of erosions occurs in 50% of patients with erosive esophagitis who are treated with H₂RAs.^{26,28}

Placebo-controlled studies demonstrate that H₂RAs provide better symptomatic relief of GERD and mucosal healing of erosive esophagitis than does placebo. Although many trials do not contain a placebo arm, Tougas and Armstrong²⁸ cited a placebo healing rate of 16.5% at 12 weeks for patients with grade II to grade IV esophagitis in a review of the efficacy of H₂RAs for treatment of GERD. That compared with a mucosal healing rate of 39.7% ($P < 0.0005$) for H₂RAs in the same review. Placebo was associated with a 13% rate of overall symptom relief,

TABLE 3
H₂RAs indicated for the treatment of GERD and their recommended nonprescription dosages³⁵

H ₂ RAs	Dosage (over-the-counter)
Nizatidine	75 mg twice daily, as needed
Famotidine	10 mg twice daily, as needed
Cimetidine	200 mg twice daily, as needed
Ranitidine	75 mg twice daily, as needed

compared with a 44% rate of overall relief with H₂RAs ($P < 0.001$). All four H₂RAs, when used at the usual recommended dose, were equally safe and effective, although their efficacy was limited in more severe forms of GERD, such as erosive esophagitis (endoscopic healing rates of 40% to 50%, symptom improvement rates of 40% to 60%).²⁸

Some non-placebo-controlled comparative studies involving H₂RAs have produced 12-week healing rates as high as 70%.²⁵ For example, a comparative study of ranitidine (150 mg two or four times daily) and cimetidine (800 mg twice daily) for the healing of erosive esophagitis demonstrated 12-week healing rates ranging from 68% to 77% (Figure 5).³² Another study of esophagitis healing found that the 6-week healing rate with ranitidine was 78% for isolated erosions but dropped to 38% for confluent erosions and to only 23% for circumferential erosions (Figure 6).³³

Tolerance

The suppression of intragastric acidity diminishes with repeated administration of H₂RAs.³⁴ A single dose of an H₂RA (Table 3)³⁵ inhibits acid secretion for approximately 4 to 8 hours and decreases stimulated acid secretion by approximately 70% in patients with esophagitis. However, H₂RA treatment has several disadvantages, including a relatively short duration of action (compared with PPIs), incomplete inhibition of acid secretion in response to a meal, and the development of tolerance. It is therefore not easy for H₂RAs to effectively heal the more severe forms of erosive esophagitis, even when very high doses are used. When severe erosive esophagitis is not present, relief of reflux symptoms has been obtained after 4 weeks using a twice-daily regimen. In grades I or II

esophagitis, healing can be achieved with any of the H₂RAs in 40% to 60% of cases in 8 weeks. This success rate can be increased to 50% to 70% by a substantial increase in dose, but this entails cost and compliance considerations.³⁶

It is possible that tolerance may develop as a result of the down-regulation of H₂-receptors. Another possibility is that there are adaptive changes in acid secretion that are stimulated by acetylcholine, gastrin, or both.

A number of clinical studies have shown that tolerance to standard H₂RAs probably develops within the first 2 weeks of therapy.³⁶ More recently, however, tolerance has been shown to develop within 72 hours when intravenous administration of ranitidine is used to control bleeding in the upper gastrointestinal tract. To avoid such tolerance, more frequent dosing of ranitidine, more careful monitoring of intragastric pH, and repeated dose adjustments would be needed.³⁷

■ PROTON PUMP INHIBITORS

Proton pump inhibitors are the most effective medical treatment for GERD. They profoundly suppress acid secretion through inhibition of H⁺,K⁺ adenosine triphosphatase (ATPase), the proton pump of the parietal cell responsible for acid production. Unlike H₂RAs, they block acid production regardless of the method of stimulation, providing a greater degree of acid suppression for a longer duration of time. All PPIs are prodrugs, so-called substituted benzimidazoles, which must be activated by acid to inhibit the proton pump. This translates into higher efficacy rates in terms of GERD symptom relief and healing of erosive esophagitis.²⁶ A once-daily, morning dose of a PPI will relieve symptoms in 83% of patients with GERD and heal erosive esophagitis in 78%.¹ Furthermore, these rates are achieved after only 4 to 8 weeks of therapy. As with H₂RAs, healing of esophagitis with PPIs correlates with the severity of esophagitis.

Excellent healing rates have been reported in even the most severe grades of esophagitis after PPI therapy.²⁶ There is a wealth of study data on the safety and efficacy of omeprazole, the first PPI approved for treatment of GERD. Other available PPIs include lansoprazole, rabeprazole, and pantoprazole. Clinical efficacy in GERD and the safety profiles among this first generation of PPIs are very similar. The newest PPI, esomeprazole, the S-isomer

TABLE 4
Possible drug interactions with PPIs resulting from metabolism via the cytochrome P450 system⁴⁰⁻⁴³

PPI	Interactions
Omeprazole	• Inhibits metabolism of phenytoin, diazepam, antipyrine, aminopyrine, and the R-isomer of warfarin • Does not inhibit metabolism of propranolol, theophylline, or the S-isomer of warfarin
Lansoprazole	• No clinically significant interactions with most drugs metabolized through the cytochrome P450 system • Increases metabolism rate of theophylline by 10%
Pantoprazole	• No clinically significant interactions with drugs metabolized through the cytochrome P450 system • No interactions with oral contraceptives
Rabeprazole	• No clinically significant interactions with drugs metabolized through the cytochrome P450 system
Esomeprazole	• No clinically significant interactions with drugs metabolized through the cytochrome P450 system

of omeprazole, has demonstrated more complete symptom relief in patients with GERD and esophageal healing for a greater proportion of patients and in a shorter time period compared with omeprazole.^{38,39}

Pharmacokinetics and pharmacodynamics

All PPIs are metabolized in the liver via the cytochrome P450 system, specifically by the CYP2C19 and CYP3A4 enzymes.⁴⁰ There are subtle differences, however, in how each PPI is metabolized within this system. An agent's preference for one enzyme over another influences the metabolic pathway and leads to differences among the PPIs in interactions with other drugs (Table 4).

Because PPIs reduce gastric acidity, they may alter the absorption of other orally administered drugs. Elevated gastric pH has the potential to affect the stability of agents that are acid-labile or alkaline-labile, as well as the absorption of agents that have pH-dependent formulations. Whether these interactions are clinically significant is more difficult to determine. However, PPIs reduce the area

under the curve (AUC) and the peak plasma levels of ketoconazole to such an extent that patients starting therapy with ketoconazole may need to discontinue PPI therapy.⁴⁰

Individual PPIs differ in clinical pharmacology. The following sections identify selected features of the clinical pharmacology of the five available PPIs.

Omeprazole is inactivated when it is exposed to gastric acid, so it has been formulated in granules that release the drug only when the pH is greater than 6.0, resulting in a bioavailability of approximately 50%. Peak plasma concentrations occur 2 to 4 hours after oral administration and increase during the first days of therapy. The plasma half-life of omeprazole is approximately 1 hour. Food intake has no effect on the drug's pharmacokinetics.⁴⁰

Omeprazole differs from other PPIs in that its bioavailability increases with repeat dosing. A single dose of omeprazole has a bioavailability of approximately 35%, which increases with repeat dosing to around 60%. Mean AUC and peak plasma concentrations also increase disproportionately between days 1 and 5 of treatment.⁴⁰

One 20-mg dose of omeprazole inhibits acid secretion by 65% after 4 to 6 hours, dropping to 25% after 24 hours. Inhibition increases after subsequent doses and plateaus after four to six doses. Steady-state inhibition varies widely among patients, ranging from 35% to 65% based on acid secretion measurements taken 24 hours after drug inhibition, and from 30% to 100% based on measurements of 24-hour gastric acidity based on intragastric pH.⁴¹ In one study, 20-mg and 40-mg doses resulted in a mean intragastric pH greater than 4.0 for approximately 42% and 62%, respectively, of a 24-hour period after 5 days of administration.⁴² In general, when larger doses of omeprazole are given, variation of acid inhibition in patients is reduced, and acid inhibition is increased.⁴¹

Lansoprazole. Like other PPIs, lansoprazole is acid-labile. The drug is rapidly absorbed, with peak plasma concentration reached only 1.7 hours after administration. Food intake with lansoprazole delays the drug's absorption.⁴⁰ Multiple dosing does not alter its pharmacokinetics. Lansoprazole's bioavailability is approximately 80%, and its elimination half-life is less than 2 hours.⁴³

Some, but not all, studies have shown that lansoprazole's ability to suppress acid secretion is dose-dependent and increases with repeated administration. In clinical trials, a 30-mg dose resulted in an

intragastric pH greater than 4.0 for 41% of a 24-hour period on the first day of administration, rising to 66% on the fifth day. A 15-mg dose yielded an intragastric pH greater than 4.0 for 22% of a 24-hour period on the first day of administration and for 49% of a 24-hour period by the fifth day. The onset of antisecretory activity also differs between doses, with the 30-mg dose causing an increase in intragastric pH in 1 to 2 hours after administration and the 15-mg dose causing an increase in 2 to 3 hours. This time decreased with repeated dosing for both dosage strengths.⁴³

Pantoprazole. All PPIs are rapidly degraded by acidic conditions, but pantoprazole is slightly more stable than omeprazole and lansoprazole under neutral conditions or conditions that are mildly acidic (pH $\approx$ 3.5 to pH $\approx$ 7.4). Pantoprazole is therefore easier to produce in intravenous form.⁴² A 40-mg dose of pantoprazole reaches peak plasma concentrations 2 to 4 hours after administration. The estimated bioavailability of 77% reflects a low first-pass hepatic extraction. Food intake delays absorption of pantoprazole. The drug's mean plasma terminal elimination half-life is 0.9 to 1.9 hours. Repeated dosing does not alter the pharmacokinetics of pantoprazole.⁴² In this way, pantoprazole is similar to lansoprazole but unlike omeprazole.

Steady-state acid inhibition by a repeated once-daily dose of pantoprazole is dose-related over the range of 20 mg to 60 mg. However, minimal additional inhibition occurs with higher doses. After 5 days of oral administration of 40 mg or 60 mg, significant reductions in basal, nocturnal, and 24-hour intragastric pH occurred. The 40-mg dose achieved an intragastric pH greater than 4.0 for approximately 41% of a 24-hour cycle after 5 days of administration.⁴²

Rabeprazole is degraded by acid in a manner similar to lansoprazole and omeprazole and is less stable at a neutral pH than other PPIs. Maximum plasma concentrations occur 3 to 4 hours after a single dose, regardless of the dosage strength. The bioavailability of rabeprazole following a 20-mg single dose is approximately 52%. Peak plasma concentrations and the AUC increase with rising dosages, but the pharmacokinetics are not altered by multiple doses. Rabeprazole's plasma half-life is similar to that of omeprazole at approximately 1 hour. The time to achieve maximum plasma concentration is significantly prolonged by food intake. This is of no clinical significance, however, as the AUC is not altered

to a significant extent. It has been suggested that the effect of food on the time to maximum plasma concentration is secondary to the effect of food in prolonging the gastric emptying time of the enteric-coated tablets.⁴⁰

The acid-suppressive effects of rabeprazole do not increase to a significant extent with increasing doses. For instance, patients with GERD achieved an intragastric pH of 4.0 or greater for approximately 16 hours after 5 days of administration of 20 mg of rabeprazole, compared with approximately 18 hours after 5 days of administration of 40 mg.⁴⁴

Esomeprazole. Discussion of esomeprazole requires brief mention of stereoisomers, which are molecules with one or more “chiral” centers that allow the possibility of forms with the same chemical formula but differing spatial arrangements. These differences can translate into clinical differences in terms of a compound’s efficacy and toxicity.

Esomeprazole is the S-enantiomer of racemic S,R-omeprazole. It has been shown to be stable, with more than 40% of each dose showing conversion to the R-isomer.⁴⁵

Esomeprazole reaches maximum plasma concentration approximately 2 hours after administration of a single dose. As with omeprazole, the bioavailability of esomeprazole is altered by repeat dosing. In clinical studies, a 20-mg dose of esomeprazole was 50% bioavailable on day 1 of administration, increasing to 68% on day 5. The total AUC increased by 90% over 5 days. With a 40-mg dose of esomeprazole, bioavailability increased from 64% on day 1 to 89% on day 5, with an AUC increase of 159%.⁴⁶ The plasma clearance rate of esomeprazole decreases from 22 L/hour to 16 L/hour over a 5-day period, and its plasma elimination half-life increases from 0.8 hours to 1.2 hours with repeat dosing.

The pharmacokinetic and pharmacodynamic profile of esomeprazole differs from that of omeprazole. Esomeprazole given daily for 5 days had a 70% higher AUC than the same dosage of omeprazole given over the same period.⁴⁷ Furthermore, although there is variability in omeprazole’s acid inhibition among individual patients, this effect is substantially reduced with esomeprazole.

Efficacy: symptom improvement

Symptom relief is the primary goal of medical therapy for GERD and is highly predictive of endoscopic healing if esophagitis is present.⁴⁸ Interestingly, the severity of a patient’s heartburn is not necessarily

predictive of the severity of erosive esophagitis that he or she experiences. This was clearly shown in a clinical trial by Venables and colleagues,⁴⁹ who found that chronic GERD symptoms were unreliable in predicting the presence of underlying esophagitis in patients at trial entry. Although patients with severe heartburn may have normal endoscopy findings, many will have undetected erosive esophagitis. This study compared the efficacy of omeprazole 10 mg or 20 mg daily with that of ranitidine 150 mg twice daily for relief of heartburn. The 20-mg omeprazole dose was the most effective initial therapy for relief of GERD symptoms.⁴⁹

Many studies have compared the effects of H₂RAs and PPIs on symptom improvement. In general, PPIs are more effective than H₂RAs and work at a faster rate. Additionally, omeprazole has been compared with other PPIs for symptom improvement in several trials. Overall, there is not a significant difference in efficacy among the PPIs; however, there is some variability in different clinical trials.

In their meta-analysis of the efficacy of GERD therapies for treating grades II through IV erosive esophagitis, Chiba and colleagues²³ showed that PPIs provide complete heartburn relief in a higher percentage of patients and at a faster rate compared with H₂RAs. They found that more patients became heartburn-free by the second week of treatment with PPIs (58.0% ± 16.9%) than by 8 weeks of therapy with H₂RAs (48.8% ± 16.2%). The speed of heartburn relief was faster with PPIs than with H₂RAs: at week 2, patients treated with PPIs became heartburn-free at a rate of 31.8% (±7.9%) per week, compared with a rate of 17.9% (±5.8%) per week for patients treated with H₂RAs (**Figure 7**).

In the same analysis, PPIs also provided the greatest overall symptom relief, as 77.4% (±10.4%) of PPI-treated patients became heartburn-free, compared with 47.6% (±15.5%) of patients treated with H₂RAs.²³

In a pair of randomized, double-blind, multicenter trials, Richter and colleagues⁵⁰ compared lansoprazole with ranitidine in 901 patients with symptomatic reflux disease confirmed by endoscopy to be nonerosive GERD. The frequency of antacid use served as an end point for evaluating these agents’ efficacy in relieving heartburn symptoms. Compared with patients who received either of two dosages of lansoprazole, patients treated with ranitidine reported ingesting antacids on a significantly higher per-

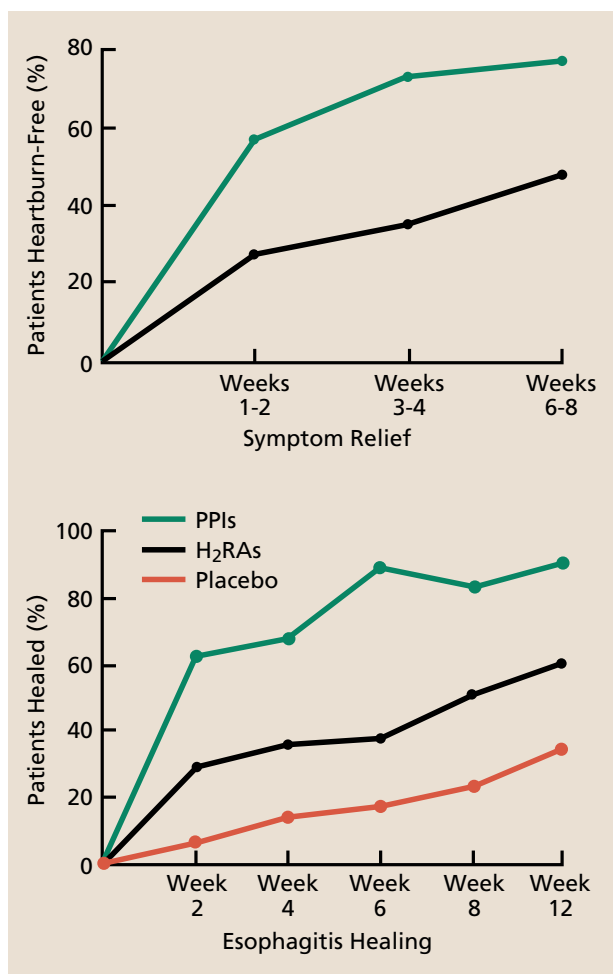


FIGURE 7. Time curves for rates of heartburn symptom relief (top) and esophagitis healing (bottom) with PPI and H₂RA therapy in a meta-analysis of efficacy trials among patients with GERD.²³ By evaluation week 2, PPIs relieved heartburn and healed esophagitis in more patients than H₂RAs did by weeks 8 or 12. Reprinted from reference 23 with permission from the American Gastroenterological Association.

centage of days (Figure 8) and ingesting a significantly higher number of antacid tablets per day. Across all treatment groups, the frequency of antacid use was associated with the frequency of days or nights with heartburn.

Variations among PPIs. Although all PPIs provide a comparably high level of symptom improvement, there are some variations in PPI performance in comparative clinical trials. Castell and colleagues⁵¹ evaluated two doses of lansoprazole (15 mg and 30 mg once daily) in comparison with omeprazole (20 mg once daily) and placebo in 1,284 patients with endoscopically confirmed erosive esophagitis.

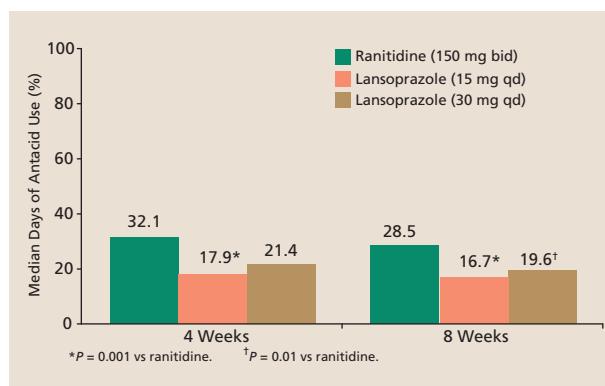


FIGURE 8. Four-week and 8-week comparisons of the median percentage of days antacids were used by patients with nonerosive GERD while receiving either ranitidine or one of two dosages of lansoprazole for relief of heartburn symptoms.⁵⁰

All PPI-treated groups experienced relief of daytime and nighttime heartburn, regurgitation, and belching to a significantly greater degree than did the placebo group, as judged by investigators and patients. Omeprazole and the 30-mg dose of lansoprazole were more effective than placebo in relieving investigator-assessed painful swallowing, whereas the 15-mg lansoprazole dose was not significantly more effective than placebo. There were no differences between the omeprazole and lansoprazole 30-mg treatment groups in investigator-assessed symptom relief, but there were differences in patient-assessed relief. After 8 weeks of therapy, patients who received omeprazole reported experiencing heartburn on 11.8% of days and 8.9% of nights during the trial, whereas those receiving 30 mg of lansoprazole reported experiencing heartburn on 8.6% of days and 6.5% of nights ($P < 0.05$ vs omeprazole). Patients receiving placebo reported experiencing heartburn on 60% of days and 45% of nights.

Mössner and colleagues⁵² investigated symptom relief in 286 patients with grades II or III erosive esophagitis randomized to receive 40 mg of pantoprazole or 20 mg of omeprazole daily for 8 weeks. Investigator-assessed symptom relief was recorded after 2 weeks and 4 weeks of therapy. Differences between the treatment groups in relieving heartburn, regurgitation, and painful swallowing were not statistically significant at 2 weeks or 4 weeks. At 2 weeks, 59% of patients receiving pantoprazole and 69% of those receiving omeprazole were symptom-free; at 4 weeks, these percentages rose to 83% and 86%, respectively (not statistically significant).

Dekkers and colleagues⁵³ compared the efficacy of

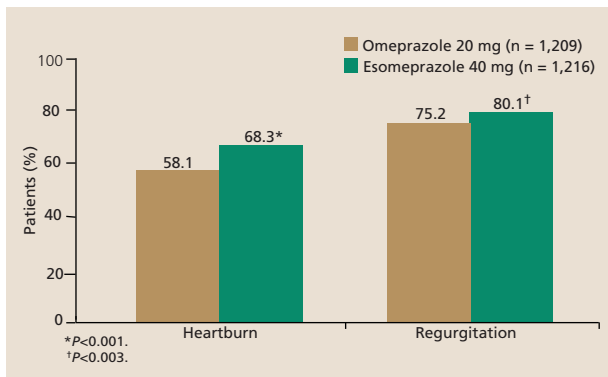


FIGURE 9. Percentages of patients with investigator-assessed resolution of GERD symptoms after 4 weeks of omeprazole or esomeprazole therapy.^{39,54}

omeprazole 20 mg daily and rabeprazole 20 mg daily in an 8-week trial in 202 patients with erosive or ulcerative reflux disease. Similar improvements in heartburn frequency rates and in daytime and nighttime heartburn severity were seen in the two treatment arms. At 8 weeks, 73% of patients receiving rabeprazole and 76% of those receiving omeprazole reported a lessening of heartburn frequency. In terms of heartburn severity, 68% of patients receiving rabeprazole reported resolution of daytime heartburn and 64% reported resolution of nighttime heartburn, which were comparable to the rates in the omeprazole group (66% and 67%, respectively).

Kahrilas and colleagues³⁸ compared symptom relief with omeprazole 20 mg daily and esomeprazole 20 mg or 40 mg daily in 1,960 patients with erosive esophagitis. After 4 weeks of therapy, esomeprazole 40 mg daily provided more effective relief of symptoms: patients who received this regimen reported experiencing no heartburn on 72.7% of days and 84.7% of nights during the trial, whereas those receiving omeprazole reported experiencing no heartburn on 67.1% of days and 80.1% of nights ($P < 0.05$). Onset of symptom relief was also faster with esomeprazole 40 mg daily, as 46.6% of patients receiving this regimen reported no heartburn on the first day of treatment, compared with 37.0% of patients receiving omeprazole.

Finally, a study by Richter and colleagues of 2,425 patients with GERD demonstrated better resolution of investigator-assessed heartburn and regurgitation after 4 weeks of treatment with esomeprazole 40 mg daily than with omeprazole 20 mg daily (Figure 9).^{39,54}

Symptom relief in nonerosive GERD. PPIs have also been tested in patients who have GERD symp-

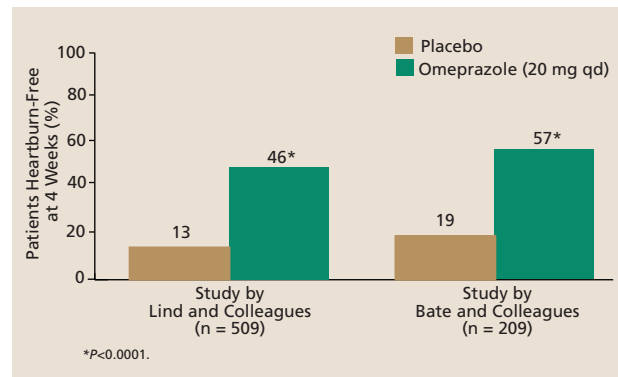


FIGURE 10. Percentages of patients with GERD but without erosive esophagitis who experienced complete relief of heartburn after 4 weeks of PPI therapy or placebo treatment.^{55,56}

toms but do not have erosive esophagitis. Lind and colleagues⁵⁵ compared omeprazole 10 mg or 20 mg daily with placebo in 509 patients with GERD but without erosive esophagitis. After 4 weeks of therapy, 46% of patients receiving omeprazole 20 mg reported complete absence of heartburn, compared with 31% of patients receiving omeprazole 10 mg and 13% of placebo recipients (Figure 10). A study by Bate and colleagues⁵⁶ of 209 patients with GERD symptoms but no esophagitis yielded similar results. This study tested only the 20-mg dose of omeprazole against placebo. After 4 weeks of therapy, 57% of patients in the omeprazole group were free of heartburn (vs 19% in the placebo group [Figure 10]), 75% experienced no regurgitation (vs 47% with placebo), and 43% were completely asymptomatic (vs 14% with placebo).

While PPIs are significantly more effective than placebo in relieving heartburn in patients with erosive esophagitis, they are not as effective in patients with nonerosive reflux disease. Carlsson and colleagues⁵⁷ conducted a 4-week comparison of two dosages of omeprazole in 277 patients with erosive esophagitis and 261 patients with GERD symptoms without erosive esophagitis. Omeprazole 10 mg daily achieved complete symptom relief in 37% of patients with erosive esophagitis, compared with 31% of patients without erosive esophagitis. Similarly, omeprazole 20 mg daily achieved complete symptom relief in 48% of patients with erosive esophagitis vs 29% of those without erosive esophagitis.

Dosage level. Dosage is an important consideration in PPI therapy. In the absence of esophagitis, when symptoms are mild or intermittent, a standard-dose PPI has been found to be effective.^{57–59} If symptoms are particularly troublesome or there is moder-

ate or severe erosive esophagitis, a twice-daily dosage may be necessary for a period of time. (However, no prospective data exist to support this recommendation.⁶⁰) Following this, dose reduction should be attempted and a plan formulated for long-term therapy. Dosage level is significant to controlling symptoms and maximizing the success of PPI therapy.⁶⁰

Nocturnal acid breakthrough. Several studies have assessed various therapeutic regimens for controlling the persistent problem of nocturnal acid breakthrough, including double-dose PPI therapy and single- or double-dose PPI therapy combined with an H₂RA. Khoury and colleagues⁶¹ found that combination therapy with 20 mg of omeprazole in the morning and 150 mg of ranitidine at night is not as effective in controlling intragastric pH as omeprazole 20 mg twice daily (one dose in the morning and one at night). In 20 healthy volunteers, the median percentage of time that intragastric pH was less than 4 when participants were upright was 29.7% in the ranitidine group and 18.9% in the double-dose omeprazole group ($P = 0.003$). The median percentages of time that intragastric pH was less than 4 when participants were recumbent were 44.75% and 23.45%, respectively ($P = 0.02$). In this study, ranitidine administered at bedtime did not eliminate the need for a second dose of omeprazole.

Peghini and colleagues⁶² compared three different regimens for controlling nocturnal acid breakthrough in 12 healthy volunteers. All participants received omeprazole 20 mg twice daily. They also received either an additional dose of omeprazole, 150 or 300 mg of ranitidine, or placebo at bedtime. Participants who received placebo at bedtime experienced an intragastric pH of less than 4 for 48% of the night. A third dose of omeprazole reduced this percentage to 31% ($P < 0.005$), but ranitidine was the most effective therapy: participants who received 150 or 300 mg of ranitidine at bedtime experienced an intragastric pH of less than 4 for only 5% and 6% of the night, respectively ($P < 0.01$ vs omeprazole 20 mg three times daily). These data suggest that double-dose PPI therapy daily plus an H₂RA at bedtime may be an effective regimen for control of nocturnal acid breakthrough.

Efficacy: healing of erosive esophagitis

In their above-mentioned meta-analysis (Figure 1), Chiba and colleagues²³ noted that PPIs were more effective than H₂RAs in treating patients with grades II through IV erosive esophagitis. PPIs pro-

vided more complete relief of symptoms and faster healing of esophagitis (Figure 7). At week 2, the healing rate per week was 31.7% ($\pm 3.3\%$) for PPIs, compared with 15.0% for H₂RAs. The healing rate per week slowed for both agents at each subsequent 2-week interval. However, PPIs maintained a therapeutic advantage because more patients were healed earlier in the course of PPI therapy, leaving fewer patients who were available to heal in later weeks. Overall, PPIs produced healing at a rate of 11.7% ($\pm 0.5\%$) per week, which was twice as fast as the healing rate per week with H₂RAs (5.9% $\pm 0.2\%$) and four times as fast as that with placebo (2.9% $\pm 0.2\%$). A mean of 83.6% ($\pm 11.4\%$) of patients with erosive esophagitis were healed with PPI therapy, compared with 51.9% ($\pm 17.1\%$) with H₂RA therapy. These numbers compare with a healing rate of 28.2% ($\pm 15.6\%$) with placebo.

A meta-analysis by Caro and colleagues⁶³ also found that PPIs were significantly more effective than H₂RAs. The investigators analyzed 53 randomized controlled trials, 38 of which involved acute therapy, although 12 of these were subsequently excluded and 15 involved maintenance treatment. Of the 26 acute therapy trials, 18 compared a PPI with an H₂RA. Of the 15 maintenance therapy trials, 5 compared a PPI with an H₂RA. No study of pantoprazole met the inclusion criteria for maintenance therapy. Combined efficacy rates from both acute and maintenance studies yielded a risk ratio that was highly favorable to PPIs.

Variations among PPIs. In the same analysis, Caro and colleagues⁶³ compared the efficacy of lansoprazole, pantoprazole, and rabeprazole with that of omeprazole and found no differences in those head-to-head comparisons. Similar results were obtained by other investigators, including teams led by Castell,⁵¹ Mössner,⁵² and Dekkers.⁵³

Although the study by Castell and colleagues⁵¹ found differences in patient-assessed symptom relief between groups receiving omeprazole 20 mg daily or lansoprazole 30 mg daily, esophageal healing rates were not statistically different between the groups. Eight-week courses of each regimen healed esophagitis in approximately 91% of patients. In the study by Mössner and colleagues,⁵² patients with esophagitis received an 8-week course of either pantoprazole 40 mg daily or omeprazole 20 mg daily. The healing rate with pantoprazole (94%) was not statistically different from that with omeprazole (90%). Finally, Dekkers and colleagues⁵³ found that an 8-week course

of rabeprazole 20 mg daily healed 92% of patients with erosive esophagitis, compared with 94% for an 8-week course of omeprazole 20 mg daily.

In the Castell study,⁵¹ lansoprazole 15 mg daily healed 79% of patients, a significantly lower percentage than those achieved with lansoprazole 30 mg daily and omeprazole 20 mg daily ($P < 0.05$). A similar dose-dependent pattern occurred in a study by Lundell and colleagues⁶⁴ between 10-mg and 20-mg doses of omeprazole. These researchers analyzed the efficacy of omeprazole in the healing of Los Angeles (LA) classification grades A through C erosive esophagitis by grade (mild through moderate-to-severe injury). With omeprazole 10 mg daily, healing efficacy was directly correlated to the grade of esophagitis: 77% of patients with grade A were healed, 50% of patients with grade B, and 20% of patients with grade C. However, this gradation in healing did not occur with omeprazole 20 mg daily, which healed roughly the same percentage (approximately 80%) of patients with grades A and B esophagitis. The 20-mg dose of omeprazole healed fewer patients with grade C esophagitis (approximately 40%) than with other grades, although it also healed more patients with this severity grade than did the 10-mg dose. A dose-related increase in healing efficacy with omeprazole was not observed, however, above the 20-mg dose.

Sontag and colleagues⁶⁵ compared 20-mg and 40-mg daily doses of omeprazole with placebo in 230 patients with GERD symptoms and erosive esophagitis. Whereas both doses of omeprazole were superior to placebo in all measures, symptom relief and esophagitis healing rates were similar in the two omeprazole groups. By the eighth week, 73.5% of patients receiving omeprazole 20 mg had complete esophageal healing, compared with 74.7% of patients receiving omeprazole 40 mg and 14.0% of placebo recipients. Omeprazole 20 mg achieved complete relief of daytime heartburn in 79.5% of patients and complete relief of nighttime heartburn in 79.5% of patients, compared with 81.6% and 85.1%, respectively, for omeprazole 40 mg, and 37.2% and 34.9%, respectively, for placebo. Although the higher dose of omeprazole resulted in faster relief of symptoms, differences between the treatment arms were not statistically significant.

A recent meta-analysis by Edwards and colleagues⁶⁶ found that esomeprazole 40 mg daily produced higher healing rates than omeprazole 20 mg daily at 4 and 8 weeks after treatment (**Figure 11**).

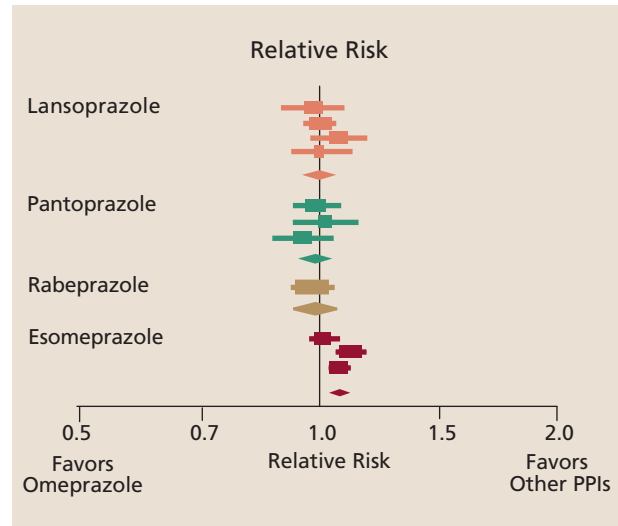


FIGURE 11. Relative risk of endoscopic healing at 8 weeks for all standard-dose PPIs compared with omeprazole 20 mg. Rectangles denote relative risk values from individual comparative trials with omeprazole; horizontal lines running through rectangles denote 95% confidence intervals. Diamonds indicate fixed effects from all comparative trials of the given PPI. Reprinted from reference 66 with permission from Blackwell Publishing.

In their analysis of 12 randomized controlled trials, these investigators found no significant differences among omeprazole and lansoprazole, pantoprazole, or rabeprazole at 4 and 8 weeks. They postulated that the superiority of esomeprazole to omeprazole may be related to its more effective suppression of intragastric acid. Recent acid-suppression studies⁶⁷ show that esomeprazole maintains intragastric pH above 4 significantly longer than lansoprazole, pantoprazole, or rabeprazole do, which may account for the differences in healing among the agents observed in this meta-analysis.

One of the studies included in the meta-analysis, conducted by Kahrilas and colleagues³⁸ (described in "Efficacy: symptom improvement" above), compared healing rates among omeprazole 20 mg daily and esomeprazole 20 mg and 40 mg daily. After 8 weeks of therapy, esomeprazole 40 mg healed esophagitis in 94.1% of patients, whereas omeprazole did so in 86.9% of patients ($P < 0.05$).

The study by Richter and colleagues³⁹ in 2,425 patients with erosive esophagitis confirmed these findings. After 8 weeks of therapy, erosive esophagitis was healed in 93.7% of patients receiving esomeprazole, compared with 84.2% of patients receiving omeprazole (by intention-to-treat analysis). Esomeprazole was more effective than omeprazole in healing

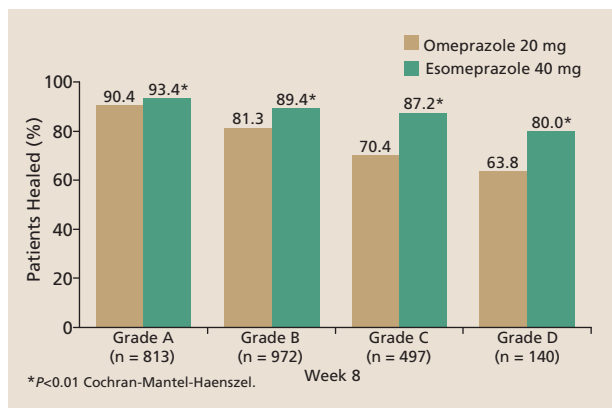


FIGURE 12. Grade-specific erosive esophagitis healing rates with omeprazole and esomeprazole therapy. Grades A and B in the Los Angeles (LA) classification represent mild to moderate esophagitis; grades C and D represent moderate to severe esophagitis.³⁹

all grades of esophagitis, as shown in **Figure 12**. Among patients with LA grades C and D esophagitis, esomeprazole healed 85.8% of patients after 8 weeks of therapy, whereas omeprazole healed 68.1%.

More recently, a study by Castell and colleagues⁶⁸ showed that esomeprazole demonstrated a slightly but significantly higher healing rate (92.6%) than lansoprazole (88.8%) at week 8. The difference in healing rates between esomeprazole and lansoprazole increased as the baseline severity of erosive esophagitis increased.

Maintenance of healing. Lauristen and colleagues⁶⁹ demonstrated that esomeprazole was more effective than lansoprazole in maintaining the healing of all grades of esophagitis (**Figure 13**). They compared esomeprazole 20 mg once daily with lansoprazole 15 mg once daily in the maintenance treatment of 1,231 patients with healed reflux esophagitis. Analysis of remission rates based on the LA classification system showed that esomeprazole maintained patients in remission more consistently across all grades of reflux esophagitis, whereas the efficacy of lansoprazole decreased to a greater extent with increasing severity of disease.

Other studies have demonstrated the low relapse rate with esomeprazole therapy over a 6-month period. In a study conducted by Johnson and colleagues⁷⁰ of 318 patients with erosive esophagitis, 40-mg and 20-mg of doses of esomeprazole once daily were highly effective at maintaining healing of erosive esophagitis over 6 months. Rates of erosive esophagitis recurrence were 6% and 7% with esomeprazole 40 mg and 20 mg, respectively, compared

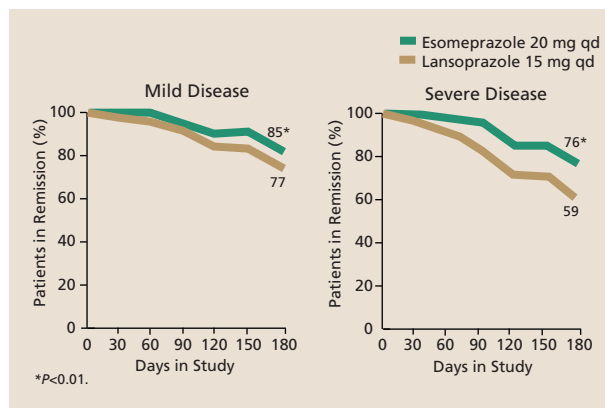


FIGURE 13. Comparison of the maintenance of erosive esophagitis healing with esomeprazole and lansoprazole therapy in patients with mild and severe disease. Reprinted from reference 69 with permission from Blackwell Publishing.

with 71% with placebo. Also, more than 70% of patients remained symptom-free at 6 months.

Table 5 presents the common dosing regimens and the efficacy rates of the available PPIs for the maintenance of erosive esophagitis healing.^{70–75}

Intravenous PPI therapy

Intravenous pantoprazole is the only PPI currently indicated in the United States for short-term treatment (7 to 10 days) of GERD in patients with a history of erosive esophagitis who are unable to take the oral formulation. In a double-blind placebo-controlled study, IV and oral pantoprazole were shown to be similar in their ability to suppress maximum and basal acid output. The study involved 65 patients with erosive esophagitis who were given 20 mg or 40 mg of oral pantoprazole for 10 days and then randomized to receive either IV pantoprazole or placebo for 7 days. Acid output was determined 24 hours after the last day of oral medication and on the first and last days of IV administration. Among patients receiving IV pantoprazole, acid suppression was comparable to that seen with oral pantoprazole and was significantly better than that achieved by patients receiving IV placebo. The recommended adult dosage of IV pantoprazole is 40 mg daily for 7 to 10 days.⁷⁶

Omeprazole has been used in injectable form in some studies around the world in an effort to prevent rebleeding following treatment for bleeding ulcers. A study in Hong Kong by Lau and colleagues³⁷ demonstrated the efficacy of omeprazole (given as an 80-mg bolus injection followed by a

continuous infusion of 8 mg/hour for 72 hours) in preventing recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. This study showed that a high-dose infusion of omeprazole reduced the rate of recurrent bleeding, decreased the need for endoscopic treatment and blood transfusions, and shortened the length of hospitalization.

Failure of therapy

Treatment of GERD with PPIs provides fast and complete relief to a larger percentage of patients than any other medical therapy. As well as PPIs work, however, they do not cure GERD and may not relieve symptoms or heal esophagitis in all patients.

Treatment with a PPI may fail in some patients because their symptoms are not caused by GERD. PPI therapy may also fail in a patient who does have GERD if the PPI dosage or the duration of therapy is insufficient to control symptoms or heal esophagitis. Therapy may also be unsuccessful if the PPI fails to control gastric acidity, although such cases are rare.^{77,78} Several reasons have been postulated for why a PPI may fail to control gastric acidity. These include oral bioavailability differences, meal timing that influences ATPase activation, increased metabolism of the PPI by the cytochrome P450 system, and hypersecretion of acid (including Zollinger-Ellison syndrome).

Patients with higher grades of esophagitis and more severe disease are less likely to experience complete healing with PPIs. A study conducted by Holloway and colleagues⁷⁹ in 61 patients with grades III or IV erosive esophagitis found that 30% of patients were not healed after 8 weeks of therapy with omeprazole 20 mg daily. These patients had greater total 24-hour esophageal acid exposure before treatment than those whose esophagitis was healed. Of those patients in whom the original course of therapy failed, 47% did not heal after 8 more weeks of therapy with a 40-mg daily dose of omeprazole. This final group of patients in whom both courses of therapy failed had levels of acid exposure before treatment that were similar to those of patients who were healed, but they had greater acid exposure during therapy, particularly at night while sleeping.

Several studies have been conducted with omeprazole to investigate the incidence of failure of PPI therapy. Leite and colleagues⁸⁰ studied 88 patients with refractory GERD symptoms who received 20 mg of omeprazole twice daily—twice the usual dose. Twenty-four-hour pH monitoring

TABLE 5
Profile of PPIs in the maintenance of erosive esophagitis healing

PPI	FDA approval date	Prescribed dose (mg/d)	Efficacy (%) [*]
Omeprazole ⁷¹	1989	10 20	58 77
Lansoprazole ⁷²	1995	15 30	67–79 55–90
Rabeprazole ⁷³	1999	10 20	75 87
Pantoprazole ⁷⁴	2000	20 40	70–72 83–86
Esomeprazole ^{70,75}	2001	20 40	93 94

^{*} In controlled clinical trials for maintenance of healing.

was used to assess results. Of the 88 patients, 17 had an intragastric pH less than 4 for more than 50% of a 24-hour period (considered failure of therapy). These 17 were then compared with 19 of the original 88 patients with GERD and with 19 healthy volunteers who received either omeprazole 20 mg twice daily or placebo. The mean intragastric pH was found to be similar between the patients with persistent symptoms who were receiving omeprazole 20 mg twice daily and the healthy subjects receiving placebo. Gastric pH monitoring in 7 patients given 80 mg of omeprazole daily, however, demonstrated a significant reduction in the mean percentage of time that the pH was less than 4, indicating that response is often a dose-dependent phenomenon.

Up to 70% of healthy subjects given twice-daily PPI therapy experience an intragastric pH less than 4 for more than 1 hour overnight (between 10:00 PM and 6:00 AM). Katz and colleagues⁸¹ noted that nocturnal acid breakthrough in patients who take omeprazole 20 mg twice daily is often accompanied by esophageal reflux and, therefore, esophageal acid exposure. Of 61 patients with GERD, 70% experienced nocturnal acid breakthrough and 33% experienced nighttime esophageal acid exposure. Of 15 patients with Barrett's esophagus, 80% experienced nocturnal acid breakthrough and 50% experienced esophageal acid exposure. In the control group (patients without GERD), these percentages were 67% (not significantly different) and 8% ($P < 0.03$), respectively. Nocturnal acid breakthrough accom-

panied by esophageal reflux in patients on twice-daily PPI therapy has important implications for medical therapy in patients with severe GERD or Barrett's esophagus.

As previously discussed, Peghini and colleagues⁶² found that the combination of an H₂RA and a PPI may be effective in managing nocturnal acid breakthrough. A recent study by Fackler and colleagues⁸² yielded differing results. The Fackler study showed that, because tolerance developed to 300 mg of ranitidine in patients with nocturnal acid breakthrough, there was no difference in acid suppression between omeprazole 20 mg twice daily and omeprazole 20 mg twice daily plus ranitidine after 1 week of combination therapy.

Safety

In general, PPIs are a remarkably safe and well-tolerated class of drugs. Headache and diarrhea are the

most frequently reported side effects, and they develop at rates that do not differ significantly from those in placebo-treated patients.⁸³ Serious side effects resulting from PPI treatment are rare. Moreover, few clinically relevant drug interactions have been reported. The PPIs' benign safety profile has contributed to their widespread prescription and use.

The long-term safety of PPIs has been a topic of some debate because most randomized controlled trials of their effects have not extended beyond 1 year. Thjodleifsson and colleagues⁸⁴ addressed this concern in a 5-year controlled trial comparing efficacy and safety between rabeprazole and omeprazole. They concluded from their results that both PPIs were safe and well tolerated during the 5-year study period, contributing to a growing body of evidence confirming the long-term safety of PPIs in acid suppression.

REFERENCES

- DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 1999; 94:1434-1442.
- Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management: the Genval Workshop Report. *Gut* 1999; 44(suppl 2):1-16.
- Ramirez B, Richter JE. Review article: promotility drugs in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1993; 7:5-20.
- Thanik KD, Chey WY, Shah AN, Gutierrez JG. Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. *Ann Intern Med* 1980; 93:805-808.
- Paull A, Grant AK. A controlled trial of metoclopramide in reflux esophagitis. *Med J Aust* 1974; 2:627-629.
- Venables CW, Bell D, Eccleston D. A double-blind study of metoclopramide in symptomatic peptic esophagitis. *Postgrad Med J* 1973; 49(suppl 4):73-77.
- McCallum RW, Ippoliti AF, Cooner C, et al. A controlled trial of metoclopramide in symptomatic gastro-esophageal reflux. *N Engl J Med* 1977; 296:354-357.
- Bright-Asare P, El-Bassoussi M. Cimetidine, metoclopramide or placebo in the treatment of symptomatic gastroesophageal reflux. *J Clin Gastroenterol* 1980; 2:149-156.
- Temple JG, Bradby GVH, O'Connor F, et al. Cimetidine and metoclopramide in esophageal reflux disease. *BMJ* 1983; 286:1863-1864.
- Guslandi M, Testoni PA, Passaretti S, et al. Ranitidine vs metoclopramide in the medical treatment of reflux esophagitis. *Hepatogastroenterology* 1983; 30:96-98.
- Tytgat GNJ, Nio CY. The medical therapy of reflux esophagitis. *Baillieres Clin Gastroenterol* 1987; 1:791-807.
- Blackwell JN, Heading RC, Fettes MR. Effects of domperidone on lower oesophageal sphincter pressure and gastro-oesophageal reflux in patients with peptic esophagitis. *Progress with domperidone*. Royal Society of Medicine. International Congress and Symposium Series 1981; 36:57-65.
- Masci E, Testoni PA, Passaretti S, Guslandi M, Tittobello A. Comparison of ranitidine, domperidone maleate, and ranitidine + domperidone maleate in the short-term treatment of reflux esophagitis. *Drugs Exp Clin Res* 1985; 11:687-692.
- Guslandi M, Dell'Oca M, Molteni V, et al. Famotidine vs domperidone, versus a combination of both in the treatment of reflux esophagitis. *Gastroenterology* 1989; 96(suppl):191A. Abstract.
- Richter JE. Cisapride: limited access and alternatives. *Cleve Clin J Med* 2000; 67:471-472.
- DeMicco M, Berenson M, Wu W, et al. Cisapride in the treatment of GERD: a double-blind, placebo-controlled multicenter dose-response trial. *Gastroenterology* 1992; 102(suppl):59A. Abstract.
- Galmiche JP, Fraitaig B, Filoche B, et al. Double-blind comparison of cisapride and cimetidine in treatment of reflux esophagitis. *Dig Dis Sci* 1990; 35:649-655.
- Elsborg L, Beck B, Stubgaard M. Effect of sucralfate on gastroesophageal reflux in esophagitis. *Hepatogastroenterology* 1985; 32:181-184.
- Katz PO, Castell DO. Gastroesophageal reflux disease during pregnancy. *Gastroenterol Clin North Am* 1998; 27:153-167.
- Simon B, Mueller P. Comparison of the effect of sucralfate and ranitidine in reflux esophagitis. *Am J Med* 1987; 83:43-47.
- Hameeteman W, van de Boogaard DM, Dekker W, et al. Sucralfate versus cimetidine in reflux esophagitis: single-blind multicenter study. *J Clin Gastroenterol* 1987; 9:390-394.
- Laitinen S, Stahlberg M, Kairaluoma MI, et al. Sucralfate and alginate/antacid in reflux esophagitis. *Scand J Gastroenterol* 1985; 20:229-232.
- Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997; 112:1798-1810.
- Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996; 10:441-446.
- Kitchin LI, Castell DO. Rationale and efficacy of conservative therapy for gastroesophageal reflux disease. *Arch Intern Med* 1991; 151:448-454.
- Klinkenberg-Knol EC, Festen HPM, Meuwissen SGM. Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995; 49:695-710.
- Furman D, Mensh R, Winan G, et al. A double-blind trial comparing high dose liquid antacid to placebo and cimetidine in improving symptoms and objective parameters in gastroesophageal

- reflux. *Gastroenterology* 1992; 82(suppl):A1062. Abstract.
28. **Tougas G, Armstrong D.** Efficacy of H₂-receptor antagonists in the treatment of gastroesophageal reflux disease and its symptoms. *Can J Gastroenterol* 1997; 11(suppl B):51–54.
29. **Lin JH.** Pharmacokinetic and pharmacodynamic properties of histamine H₂-receptor antagonists: relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet* 1991; 20:218–236.
30. **Hallerback B, Glise H, Johansson B, et al.** Gastro-oesophageal reflux symptoms: clinical findings and effect of ranitidine treatment. *Eur J Surg Suppl* 1998; 583:6–13.
31. **Kahrilas PJ, Fennerty MB, Joelsson B.** High- versus standard-dose ranitidine for control of heartburn in poorly responsive acid reflux disease: a prospective, controlled trial. *Am J Gastroenterol* 1999; 94:92–97.
32. **McCarty-Dawson D, Sue SO, Morrill B, Murdock RH.** Ranitidine versus cimetidine in the healing of erosive esophagitis. *Clin Ther* 1997; 18:1150–1160.
33. **Koelz HR, Bircher R, Bretholz A, et al.** Healing and relapse of reflux esophagitis during treatment with ranitidine. *Gastroenterology* 1986; 91:1198–1205.
34. **Wilder-Smith C, Halter F, Ernst T, et al.** Loss of acid suppression during dosing with H₂-receptor antagonists. *Aliment Pharmacol Ther* 1991; 4(suppl 1):15–27.
35. **Scott M, Gelhot A.** Gastroesophageal reflux disease: diagnosis and management. *Am Fam Phys* 1999; 59:1161–1169.
36. **Colin-Jones DG.** The role and limitations of H₂-receptor antagonists in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1995; 9(suppl 1):9–14.
37. **Lau JYW, Sung JY, Lee KKC, et al.** Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcer. *N Engl J Med* 2000; 343:310–316.
38. **Kahrilas PJ, Falk GW, Johnson DA, et al.** Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux esophagitis patients: a randomized controlled trial. *Aliment Pharmacol Ther* 2000; 14:1249–1258.
39. **Richter JE, Kahrilas PJ, Johanson J, et al.** Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001; 96:656–665.
40. **Lew EA.** Review article: pharmacokinetic concerns in the selection of anti-ulcer therapy. *Aliment Pharmacol Ther* 1999; 13(suppl 5):11–16.
41. **Maton PN.** Omeprazole. *N Engl J Med* 1991; 324:965–975.
42. **Fittion A, Wiseman L.** Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. *Drugs* 1996; 51:460–482.
43. **Physicians Desk Reference.** 54th ed. Montvale, N.J.: Medical Economics Company; 2000.
44. **Robinson M, Sloan S, Gardner J, Barth J.** Gastric acid suppression by rabeprazole: how much is enough to normalize exophageal acid exposure in gastroesophageal reflux disease? *Gastroenterology* 1996; 116(suppl):A292–A293.
45. **Hassan-Alin M, Nizai M, Röhss K, et al.** Esomeprazole, the S-isomer of omeprazole, is optically stable in humans. *Gastroenterology* 2000; 118(suppl):A1244–A1245. Abstract.
46. **Hassan-Alin M, Röhss K, Andersson T, Nyman L.** Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. *Gastroenterology* 2000; 118(suppl):A16. Abstract.
47. **Spencer CM, Faulds D.** Esomeprazole. *Drugs* 2001; 60:321–329.
48. **Carlsson R, Galmiche J-P, Dent J, et al.** Prognostic factors influencing relapse of esophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997; 11:473–482.
49. **Venables TL, Newland RD, Patel AC, et al.** Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1997; 32:965–973.
50. **Richter JE, Campbell DR, Kahrilas PJ, et al.** Lansoprazole compared with ranitidine for the treatment of nonerosive gastro-oesophageal reflux disease. *Arch Intern Med* 2000; 160:1803–1809.
51. **Castell DO, Richter JE, Robinson M, et al.** Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. *Am J Gastroenterol* 1996; 91:1749–1757.
52. **Mössner J, Hölscher AH, Herz R, Schneiders A.** A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther* 1995; 9:321–326.
53. **Dekkers CPM, Beker JA, Thjodleifsson B, et al.** Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1999; 13:49–57.
54. **Richter JE, Kahrilas PJ, Hwang C, Marino V, Hamelin B.** Esomeprazole is superior to omeprazole for the healing of erosive esophagitis in GERD patients. *Gastroenterology* 2000; 118(4 suppl 2):A20. Abstract 343.
55. **Lind T, Havelund T, Carlsson O, et al.** Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997; 32:974–979.
56. **Bate CM, Griffin SM, Keeling PWN, et al.** Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. *Aliment Pharmacol Ther* 1996; 10:547–555.
57. **Carlsson R, Dent J, Watts R, et al.** Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. *Eur J Gastroenterol Hepatol* 1998; 10:119–124.
58. **Lind T, Havelund T, Lundell L, et al.** On-demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis—a placebo-controlled randomized trial. *Aliment Pharmacol Ther* 1999; 13:907–914.
59. **Talley NJ, Lauritsen K, Tunturi-Hihnalas H, et al.** Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Aliment Pharmacol Ther* 2001; 15:347–354.
60. **Tygat GNJ.** Review article: treatment of mild and severe cases of GERD. *Aliment Pharmacol Ther* 2002; 16(suppl 4):73–78.
61. **Khouri RM, Katz PO, Hammoud R, Castell DO.** Bedtime ranitidine does not eliminate the need for a second daily dose of omeprazole to suppress nocturnal gastric pH. *Aliment Pharmacol Ther* 1999; 13:675–678.
62. **Peghini PL, Katz PO, Castell DO.** Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. *Gastroenterology* 1998; 115:1335–1339.
63. **Caro JJ, Salas M, Ward A.** Healing and relapse rates in gastro-oesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther* 2001; 23:998–1017.
64. **Lundell LR, Dent J, Bennett JR, et al.** Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; 45:172–180.
65. **Sontag SJ, Hirschowitz BJ, Holt S, et al.** Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the US multicenter study. *Gastroenterology* 1992; 102:109–118.
66. **Edwards SJ, Lind T, Lundell L.** Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment Pharmacol Ther* 2001; 15:1729–1736.
67. **Röhss K, Wilder-Smith C, Claar-Nilsson C, et al.** Esomeprazole 40 mg provides more effective acid control than standard doses of all other proton pump inhibitors. *Gastroenterology* 2001; 120(suppl):A419. Abstract.
68. **Castell DO, Kahrilas MD, Richter JE, et al.** Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *Am J Gastroenterol* 2002; 97:575–583.
69. **Lauritsen K, Devière J, Bigard M-A, et al.** Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux esophagitis:

- Metropole study results. *Aliment Pharmacol Ther* 2003; 17:333–341.
70. **Johnson DA, Benjamin SB, Whipple J, D'Amico D, Hamelin B.** Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol* 2001; 96:27–34.
71. **Prilosec** [package insert]. Wilmington, Del.: AstraZeneca Pharmaceuticals LP; 2002.
72. **Prevacid** [package insert]. Lake Forest, Ill.: TAP Pharmaceutical Products Inc.; 2002.
73. **Aciphex** [package insert]. Teaneck, N.J.: Eisai Inc.; 2002.
74. **Protonix** [package insert]. Philadelphia: Wyeth Laboratories; 2003.
75. **Nexium** [package insert]. Wilmington, Del.: AstraZeneca Pharmaceuticals LP; 2003.
76. **Protonix IV** [package insert]. Philadelphia: Wyeth Pharmaceuticals Inc.; 2003.
77. **DeVault KR, Castell DO.** Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Arch Intern Med* 1995; 155:2165–2173.
78. **Freston JW.** The management of gastroesophageal reflux disease in the era of proton pump inhibitors. *Pract Gastroenterol* 1994; 28(suppl):S24–S30.
79. **Holloway RH, Dent J, Narielvala F, Mackinnon AM.** Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. *Gut* 1996; 38:649–654.
80. **Leite LP, Johnston BT, Just RJ, Castell DO.** Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. *Am J Gastroenterol* 1996; 91:1527–1531.
81. **Katz PO, Anderson C, Khoury R, Castell DO.** Gastro-oesophageal reflux associated with nocturnal gastric acid breakthrough on proton pump inhibitors. *Aliment Pharmacol Ther* 1998; 12:1231–1234.
82. **Fackler WK, Ours TM, Vaezi MF, Richter JE.** Long-term effect of H₂RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology* 2002; 122:625–632.
83. **Spechler SJ.** In: Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed. Philadelphia: Saunders; 2002:747–781.
84. **Thjodleifsson B, Rindi G, Fiocca A, et al.** A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg rabeprazole compared with 20 mg omeprazole in the maintenance of gastro-oesophageal reflux disease over 5 years. *Aliment Pharmacol Ther* 2003; 17:343–351.