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Proton-pump inhibitors for gastric acid-related disease

ABSTRACT

Proton-pump inhibitors are the most effective drugs introduced to date for suppressing gastric acid production. Although they are used to treat the same conditions as histamine type-2 receptor antagonists, they differ from the latter drugs in how they inhibit acid production, and in how they should be given. Initial concerns over potential ill effects of hypergastrinemia due to long-term acid suppression with proton-pump inhibitors have been unfounded.

KEY POINTS

Proton-pump inhibitors provide superior rates of healing and symptom relief compared with histamine type-2 receptor antagonists. The inhibition of gastric acid secretion is dose-dependent and long-lasting.

The adverse effect profile of proton-pump inhibitors is comparable to that of the histamine type-2 receptor antagonists.

Proton-pump inhibitors are given once daily. Taking liquid antacids concomitantly does not affect omeprazole absorption.

PROTON-PUMP INHIBITORS, the most effective drugs introduced to date for suppressing gastric acid production, have improved the treatment of acid-related gastrointestinal disease.[1] Compared with histamine type-2 (H_2) receptor antagonists, they provide superior healing rates and symptom relief in peptic ulcer disease,[2–9] reflux esophagitis,[10–13] and Zollinger-Ellison syndrome.[14,15]

Although the two available proton-pump inhibitors—omeprazole, approved by the US Food and Drug Administration in 1989, and lansoprazole, approved in 1995—are used to treat the same conditions as H_2 receptor antagonists, they differ in how they should be given. There are also a few minor but noteworthy differences between the two proton-pump inhibitors. In the following update we review the characteristics of proton-pump inhibitors and look at how omeprazole and lansoprazole differ from each other.

Another proton-pump inhibitor, pantoprazole, is available in Europe and is in clinical trials in the United States for gastroesophageal reflux disease and ulcer disease. Its clinical efficacy appears similar to the other proton-pump inhibitors. Pending US Food and Drug Administration approval, pantoprazole should be available in the next 2 years.

Perprazole, an optical isomer of omeprazole, is also under investigation. It is purported to have unique pharmacokinetic properties that may lead to rapid resolution of symptoms and high, predictable healing rates. A new drug application is expected to be filed within the next 2 years. Perprazole will be available in a new oral dosage form called the "multiunit pellet system." This is a tablet that is easier to swallow because it can be halved or dissolved in water for liquid dosing.

HOW DO PROTON-PUMP INHIBITORS WORK?

Instead of blocking the primary stimuli of gastric acid secretion (ie, food, gastrin, histamine), the proton-pump inhibitors directly block the final step of gastric acid production, ie, the hydrogen-potassium ATPase[16] enzyme system on the secretory surface of gastric parietal cells—the "acid (proton) pump" (FIGURE 1).

The inhibition of gastric acid secretion caused by proton-pump inhibitors is dose-dependent and long-lasting, because these drugs bind permanently to hydrogen-potassium ATPase molecules. Because secretion of acid can resume only after new molecules of hydrogen-potassium ATPase are generated, the inhibition persists long after the drug is cleared from the plasma. It is this thorough and lasting inhibition that enables proton-pump inhibitors to accelerate ulcer healing. Although the plasma elimination half-life is less than 2 hours, the acid-inhibitory effect lasts more than 24 hours.

INDICATIONS FOR PROTON-PUMP INHIBITORS

Omeprazole indications

- Active duodenal ulcer.
- Active duodenal ulcer with *Helicobacter pylori* infection for which omeprazole is given in combination with clarithromycin.
- Active benign gastric ulcer.
- Erosive esophagitis (short-term and long-term treatment).
- Symptomatic gastroesophageal reflux disease, regardless of the presence of esophagitis.
- Hypersecretory conditions, ie, Zollinger-Ellison syndrome (long-term treatment).

Inhibition of gastric acid secretion by proton-pump inhibitors is dose-dependent and long-lasting

Lansoprazole indications

- Active duodenal ulcer.
- Active duodenal ulcer with *H pylori* infection, for which lansoprazole is given in combination with clarithromycin or amoxicillin or both.
- Erosive esophagitis.
- Active benign gastric ulcer.
- Zollinger-Ellison syndrome (long-term treatment).

US Food and Drug Administration approval for the use of lansoprazole in gastroesophageal reflux disease is pending.

How proton-pump inhibitors compare with histamine-2 receptor antagonists

Proton-pump inhibitors provide superior healing rates and symptom relief compared with H_2 receptor antagonists.

- In patients with duodenal and gastric ulcer, 4-week healing rates were 69% to 100% in clinical trials, compared with 58% to 89% for H_2 receptor antagonists.[2–9]
- In reflux esophagitis, 8-week healing rates were 70% to 92%, compared with 29% to 70% for H_2 receptor antagonists.[10–13]
- In Zollinger-Ellison syndrome,[15,16] a gastric acid output of less than 10 mmol/hour before the next dose is given is universally accepted as the guide to effectiveness of therapy. Relief of symptoms is an unreliable guide. Gastric acid secretion can be controlled (<10 mmol/hour at the end of the dosing interval) by one or two daily doses of a proton-pump inhibitor, while H_2 receptor antagonists at high doses are required four to six times per day.

Proton-pump inhibitors have also proven effective in peptic ulcer disease and reflux esophagitis refractory to treatment with H_2 receptor antagonists in standard and high doses, with 8-week healing rates ranging from 80% to 96%.[17–27] They also appear to prevent the recurrence of lesions when given as maintenance therapy in refractory reflux esophagitis.[13,23,26,28,29]

ADVERSE REACTIONS OF PROTON-PUMP INHIBITORS

Both omeprazole and lansoprazole are generally well tolerated, with an incidence of adverse effects similar to those of H_2 receptor antagonists in comparative studies.[30,31] Adverse effects from proton-pump inhibitors appear to be unrelated to dosage or patient age.

Omeprazole side effects

Gastrointestinal side effects were most frequently reported[32]: diarrhea in 1.9% of patients in the treatment group, flatulence 1.6%, nausea 0.9%, constipation 0.5%, and abdominal pain 0.4%.

Central nervous system reactions were the next most frequently reported[32]: headache 2.4%, dizziness or vertigo 0.5%.

Acid production and inhibition in the gastric parietal cell

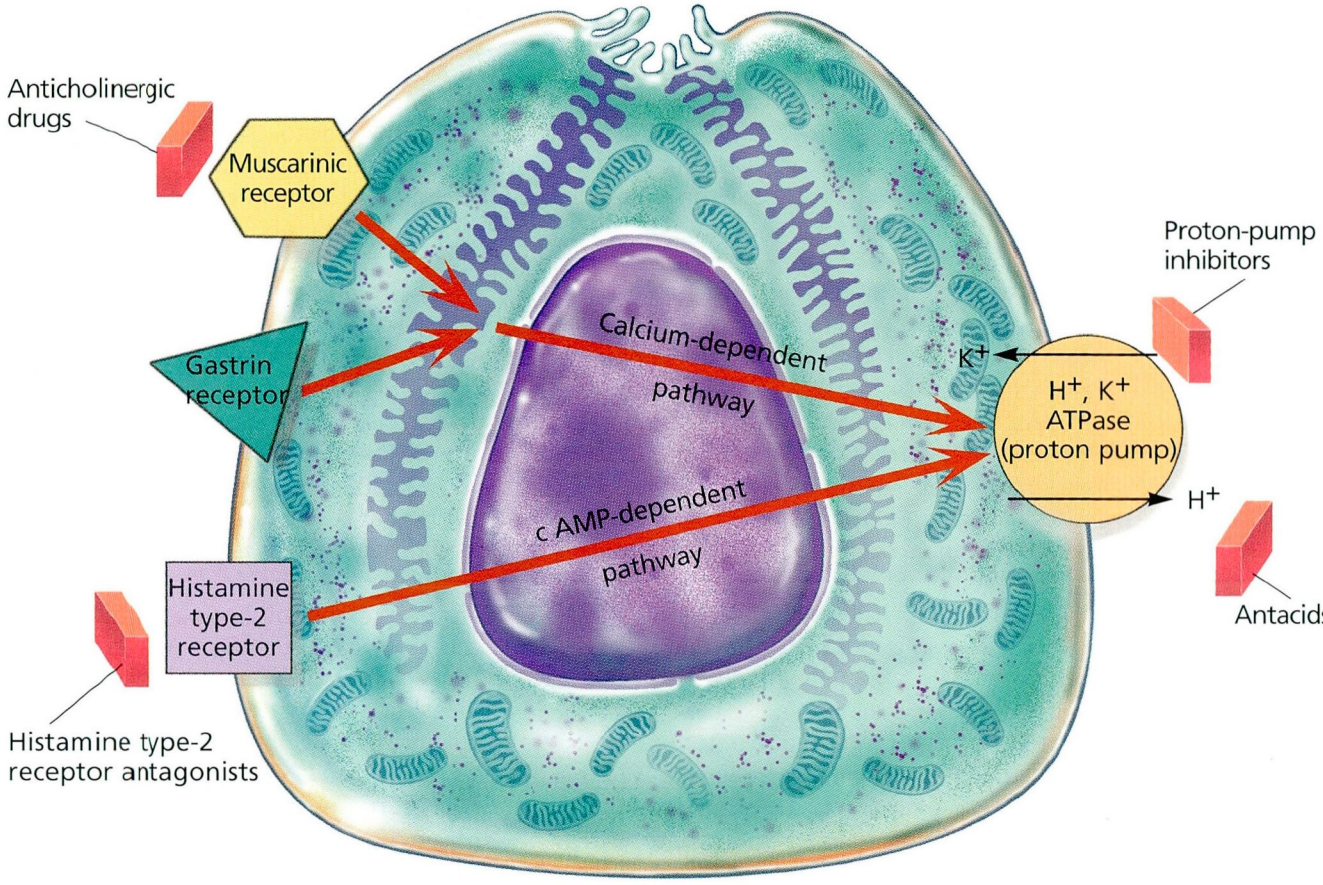

FIGURE 1. Rather than block one or another of the primary stimuli of gastric acid production (eg, histamine, gastrin, muscarinic receptors), proton-pump inhibitors stop acid secretion by inhibiting the final common pathway of acid production: the acid proton pump, hydrogen-potassium ATPase, on the surface of the gastric parietal cell. In contrast, anticholinergic drugs block muscarinic receptors, which normally activate the proton pump via the calcium-dependent pathway. Histamine type-2 receptor antagonists block histamine receptors, which normally activate the proton pump via the cyclic adenosine monophosphate (cAMP) pathway. Antacids interact with hydrochloric acid to increase the gastric pH; gastric acid activity decreases as the pH rises.

In addition to these, a few cases of skin rash have been reported (0.5% to 1%).[32,33] Idiosyncratic adverse effects were also reported: gynecomastia, 3 cases; lichen planus, 1 case; subacute myopathy, 1 case; sexual disturbances, 2 cases; renal failure, 1 case; acute interstitial nephritis, 1 case; and fulminant hepatic failure, 1 case.[34] Fewer than 2% of patients treated with omeprazole have withdrawn from clinical trials because of adverse events. The adverse event profile of long-term omeprazole use (up to 6 years) was reported to be similar to that of short-term omeprazole therapy.[31]

Lansoprazole side effects

Patients have received lansoprazole for up to 4 years in clinical trials without experiencing significant adverse effects. Lansoprazole is clinically well tolerated. The most common reported adverse reactions[35] are gastrointestinal: diarrhea 3.2%, abdominal pain 2.2%, nausea 1.4%, and constipation 1.1%. Central nervous system reactions are the next most frequently reported, with headache 4.7% and dizziness 1%. As with omeprazole, skin disorders such as rash and pruritus have also been reported in 1.7% of patients.

Increases in liver enzymes, hemoglobin, hematocrit, urinary protein excretion, and uric acid levels have been reported. Fewer than 1.2% of patients treated with lansoprazole withdrew because of adverse events.[35]

Omeprazole and lansoprazole are well tolerated, with an incidence of adverse effects similar to those of H_2 receptor antagonists

Concerns over long-term treatment

A consequence of the rigorous inhibition of gastric acid secretion produced by proton-pump inhibitors is achlorhydria, the absence of free hydrochloric acid. There was concern early on that sustained achlorhydria induced by proton-pump inhibitors could result in elevated serum gastrin concentrations, which in turn could produce carcinoid tumors; however, this has not been shown to be a problem, either with long-term omeprazole use in the United States or with long-term lansoprazole use in Europe.[36] Achlorhydria produced by proton-pump inhibitors has led to hypergastrinemia and carcinoid tumors only in rats; these findings have not been shown to occur in other animal species (humans, dogs, guinea pigs, hamsters, mice).[37–39]

DRUG INTERACTIONS

Omeprazole drug interactions

Omeprazole can bind to hepatic cytochrome P450 IIC and inhibit the oxidative metabolism of diazepam and phenytoin, leading to increased plasma levels of these drugs. However, the omeprazole-diazepam and omeprazole-phenytoin interactions are of limited clinical significance. Furthermore, since few drugs are metabolized mainly by cytochrome P450 IIC, the potential for omeprazole to interfere with the metabolism of other drugs appears to be limited.[40]

Omeprazole also appears to inhibit the hepatic metabolism of the R-isomer of warfarin (which is pharmacologically less active than the S-isomer), resulting in a slight increase in anticoagulation activity. As with the interactions cited above, studies show that this is not likely to be of clinical significance,[41,42] but a single case report indicates that certain individuals may exhibit clinically important increases.[43]

Proton-pump inhibitors can inhibit the absorption of drugs such as griseofulvin, ketoconazole, itraconazole, iron salts, and cyanocobalamin, which require acid for absorption. Conversely, drugs normally destroyed by gastric acid (penicillin, didanosine) may show increased absorption.

Interaction with clarithromycin. Concomitant administration of omeprazole and clarithromycin may result in increased serum concentrations of both drugs. Also, the gastric mucous concentration of clarithromycin may be increased. Clarithromycin may inhibit the metabolism (via cytochrome P450 IIIA4) of omeprazole, while omeprazole may increase the absorption of clarithromycin. The concomitant administration of these agents may be beneficial in the treatment of *H pylori* infections. No adjustment in dosage is necessary for either agent.[44]

Lansoprazole drug interactions

The metabolism of lansoprazole also involves the hepatic cytochrome P450 enzyme system, but lansoprazole does not appear to significantly interact with other drugs metabolized by this system.[45]

TABLE 1

Dosage recommendations for proton-pump inhibitors

INDICATION	OMEPRAZOLE	LANSOPRAZOLE
Duodenal ulcer	20 mg/day up to 4 weeks	15 mg/day up to 4 weeks
Gastric ulcer	20 mg/day up to 8 weeks	30 mg/day up to 8 weeks
Reflux esophagitis		
Short-term therapy	20 mg/day up to 8 weeks	30 mg/day up to 8 weeks
Maintenance therapy	20 mg/day	15 mg/day
Resistant ulcer	40 mg/day up to 8 weeks*	30 mg/day up to 8 weeks
Zollinger-Ellison syndrome†	60 mg/day§	60 mg/day‡

*Twice-daily dosing (doses ≥ 40 mg/day) provides better gastric acid suppression compared with once-daily dosing[50]
†Titrate for a basal acid output < 10 mmol/h prior to next dose
‡May be increased up to 90 mg twice daily if necessary
§May be increased up to 180 mg twice daily if necessary

No clinically significant interactions have been reported to date in the 2 years since lansoprazole has been available in the United States. As described above with omeprazole, lansoprazole may adversely affect medications requiring acid for absorption, while increasing absorption of medications normally destroyed by gastric acid.

BIOAVAILABILITY

Omeprazole bioavailability[46] increases with repeated administration, suggesting that either absorption increases or first-pass hepatic metabolism becomes saturated, or both. Food delays the rate, but not the extent, of omeprazole absorption. Concomitant administration with liquid antacids has no effect on omeprazole absorption.

Lansoprazole bioavailability decreases 27% when given with a meal,[45] but gastric acidity reduction was found to be similar whether lansoprazole was given 30 minutes before or 30 minutes after a meal for 7 days. Concomitant administration of antacids resulted in a small decrease in lansoprazole absorption. Concurrent administration of lansoprazole and sucralfate reduced lansoprazole's bioavailability by 30%.

DOSAGE AND ADMINISTRATION

Proton-pump inhibitors are long-acting, permitting once-daily dosing. Both omeprazole and lansoprazole are available as delayed-release capsules.

Omeprazole is available as 10- and 20-mg capsules. It is usually given in the morning before breakfast. The recommended dosages are 20 mg daily for 2 to 8 weeks for reflux esophagitis or duodenal or gastric ulcers. A dosage of 40 mg daily may be required in patients with conditions poorly responsive to H_2 receptor antagonists or in patients in whom ulcers have not healed with omeprazole 20 mg daily (TABLE 1). With higher doses (40 mg per day or more), a twice-daily dosing regimen (before breakfast and dinner) may provide better acid control than once-daily dosing.[47]

For patients with Zollinger-Ellison syndrome, omeprazole 60 mg given daily and titrated to patient response is recommended, although lower doses (10 to 40 mg per day) are effective. For complicated reflux esophagitis, omeprazole 20 mg daily is approved for long-term maintenance therapy. Dosage reductions have not been reported necessary in patients with hepatic or renal impairment, or in the elderly.

Lansoprazole is available as 15-mg and 30-mg capsules. Like omeprazole, it is generally given in the morning before breakfast. The recommended dosage is 15 or 30 mg daily for 2 to 8 weeks for reflux esophagitis or duodenal or gastric ulcer (TABLE 1). In lesions refractory to H_2 receptor antagonist therapy, lansoprazole 30 to 60 mg per day for 8 to 12 weeks may be required. Lansoprazole 60 mg daily titrated to patient response (15 to 180 mg per day) is effective in Zollinger-Ellison syndrome. For complicated reflux esophagitis, lansoprazole 15 mg daily is approved for long-term maintenance therapy. Lansoprazole 30 mg daily was reported not to be more effective than 15 mg daily for maintenance therapy.[48] No dosage adjustment has been reported to be necessary in patients with hepatic or renal impairment, or in the elderly.

Advising patients on how to take the capsules

Omeprazole and lansoprazole are stable at neutral pH, but are destroyed by gastric acid. Therefore, patients not able to swallow capsules may be instructed to break open the gelatin-coated capsule and mix the contents with a small amount of fruit juice or applesauce immediately before oral administration. Patients should be advised not to crush the enteric-coated grains by stirring or chewing, as this exposes the drug to premature breakdown by gastric acid in the stomach.[49]

Proton-pump inhibitors directly block the final step of gastric acid production

THE ROLE OF PROTON-PUMP INHIBITORS IN *H PYLORI* ERADICATION

Duodenal or gastric ulcers unrelated to the use of nonsteroidal anti-inflammatory drugs are most often related to *H pylori* infection. All patients with active ulcer disease should be tested for *H pylori* infection, by blood serology or by tissue sampling at the time of endoscopy for histologic examination or urease test for *H pylori*. If infection is found, treatment should be started with:

- An acid-suppressing drug, to allow the ulcer to heal.
- A double-drug or triple-drug antibiotic regimen to eradicate *H pylori*. Examples are tetracycline plus metronidazole and bismuth subsalicylate, or clarithromycin plus metronidazole or amoxicillin.

After the ulcer has healed, confirming *H pylori* infection is optional in patients with no complications. Patients with bleeding and postoperative patients should be retested. *H pylori* infection is best confirmed by the newly available urea breath test (Meretek Diagnostics, Nashville, TN; Tri-Med Specialties, Charlottesville, VA). After ulcer healing and *H pylori* eradication, the proton-pump inhibitor can be stopped.

Lansoprazole has been reported to significantly affect the accuracy of the ^{14}C-urea breath test (Tri-Med Specialties) by a pH-dependent mechanism causing equivocal or false-negative results in 61% of patients.[50] Proton-pump inhibitors should be stopped at least 5 days before testing, or as recommended by the test manufacturer.

Fewer than 8% of *H pylori*-negative patients experience ulcer recurrence within 1 year after all acid-suppressive therapy has been discontinued.[51]

Reducing the risk of gastric atrophy

In patients with gastroesophageal reflux disease and *H pylori* infection, long-term therapy with a proton-pump inhibitor can result in more severe gastritis and, after 5 years of treatment, can lead to gastric atrophy in 31% of patients. Gastric atrophy is thought to be an essential step in the cascade of events leading to gastric cancer. *H pylori* detection and eradication are therefore indicated in patients with gastrointestinal esophageal reflux disease who will be undergoing long-term treatment with a proton-pump inhibitor.[52]

THE AUTHORS' PERSPECTIVE

Proton-pump inhibitors are a major advance in the treatment and management of acid-related disease. Superior healing and symptom relief, including relief in those conditions poorly responsive to H_2 receptor antagonist therapy, make them agents of choice. Proton-pump inhibitors have demonstrated a short- and long-term safety profile similar to that of H_2 receptor antagonists.

Proton-pump inhibitors cost more than H_2 receptor antagonists (TABLE 2), but they appear to be more cost-effective due to their

superior efficacy in short-term treatment of duodenal and gastric ulcer, as well as short- and long-term treatment of complicated reflux esophagitis.[53–55] The improved cost-effectiveness is due to shorter treatment periods and lower follow-up costs associated with treatment failures. Compared with each other, lansoprazole and omeprazole appear to be equally safe and effective. Lansoprazole may be somewhat less expensive than omeprazole (TABLE 2).

Proton-pump inhibitors are gradually replacing H_2 receptor antagonists in the physician's armamentarium for the treatment of acid-related diseases. This evolution has been hastened by the ready availability of over-the-counter H_2 receptor antagonists. H_2 receptor antagonists may still be a reasonable alternative in patients with gastroesophageal reflux disease characterized by mild symptoms and minimal to no esophagitis or mild, uncomplicated peptic ulcer disease.

TABLE 2

Cost of proton-pump inhibitors compared with histamine type-2 receptor antagonists

MEDICATION	DOSAGE	COST*	
		4 WEEKS	8 WEEKS
Histamine type-2 receptor antagonists			
Cimetidine†	800 mg/day	$83.65	$167.30
Famotidine	40 mg/day	$95.86	$191.72
Nizatidine	300 mg/day	$96.00	$192.00
Ranitidine†	300 mg/day	$88.80	$177.60
Proton-pump inhibitors			
Lansoprazole	30 mg/day	$102.68	$205.36
	15 mg/day	$100.75	$201.50
Omeprazole	20 mg/day	$108.90	$217.80
	10 mg/day	$97.56	$195.12

*Average wholesale price, Red Book, 1996
†Generic product

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