

# Proton Pump Inhibitors: An Update

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Since their introduction in the late 1980s, proton pump inhibitors have demonstrated gastric acid suppression superior to that of histamine H<sub>2</sub>-receptor blockers. Proton pump inhibitors have enabled improved treatment of various acid-peptic disorders, including gastroesophageal reflux disease, peptic ulcer disease, and nonsteroidal anti-inflammatory drug-induced gastropathy. Proton pump inhibitors have minimal side effects and few significant drug interactions, and they are generally considered safe for long-term treatment. The proton pump inhibitors omeprazole, lansoprazole, rabeprazole, and the recently approved esomeprazole appear to have similar efficacy. (*Am Fam Physician* 2002;66:273-80. Copyright© 2002 American Academy of Family Physicians.)

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Proton pump inhibitors (PPIs) are one of the most commonly prescribed classes of medications in the primary care setting and are considered a major advance in the treatment of acid-peptic diseases. Since the introduction of omeprazole (Prilosec) in 1989, several other PPIs have become available in the United States. The intravenous form of pantoprazole (Protonix I.V.) is now available, and the U.S. Food and Drug Administration (FDA) approved the newest PPI, esomeprazole (Nexium), in 2001.

## Basic Pharmacology

PPIs are substituted benzimidazoles and are generally administered as enteric-coated tablets or capsules that pass through the stomach intact and are absorbed in the proximal small bowel. Once absorbed, all PPIs have a relatively short plasma half-life (about one to two hours). Their duration of action is much longer because of their unique mechanism of action. PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the PPI becomes protonated, producing the activated sulphenamide form

of the drug that binds covalently with the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme that results in irreversible inhibition of acid secretion by the proton pump.<sup>1-3</sup> The parietal cell must then produce new proton pumps or activate resting pumps to resume its acid secretion.<sup>1,2</sup>

In contrast to the other PPIs, rabeprazole (Aciphex) forms a partially reversible bond with the proton pump and is activated at a broader range of gastric pH. Therefore, it may have a more sustained acid-suppressing effect than the other PPIs.<sup>1,2,4</sup> *Table 1*<sup>2</sup> outlines the pharmacokinetic profiles of four orally administered PPIs.

## Side Effects and Precautions

PPIs are generally well tolerated. The frequency of adverse effects associated with PPIs is similar to that of placebo, with an overall incidence of less than 5 percent.<sup>5</sup> The type and frequency of adverse effects are similar to those observed with histamine H<sub>2</sub>-receptor blockers. The most common adverse effects are headache, diarrhea, abdominal pain, and nausea. Except for diarrhea, the adverse effects of PPIs do not appear to be related to age, dosage, or duration of treatment.<sup>5,6</sup> The diarrhea seems to be related to the profound acid suppression, which has been shown to alter the bacterial content of the gut. Nevertheless, the overall incidence of diarrhea is less than 5 percent, and this effect appears to be dosage- and age-related.<sup>5</sup>

Short-term safety (less than 12 weeks of treatment) of the oldest agents, omeprazole

*The frequency of adverse effects associated with proton pump inhibitors is similar to that of placebo, with an overall incidence of less than 5 percent.*

**TABLE 1**  
**Pharmacokinetic Profiles of Four Orally Administered PPIs**

Characteristic	Omeprazole (Prilosec)	Lansoprazole (Prevacid)	Rabeprazole (Aciphex)	Pantoprazole (Protonix)
Bioavailability (%)	30 to 40	80 to 85	52	77
Time to peak plasma concentration (hours)	0.5 to 3.5	1.7	1.0 to 2.0	1.1 to 3.1
Plasma elimination half-life (hours)	0.5 to 1.0	1.3 to 1.7	1.0 to 2.0	1.0 to 1.9
Protein binding (%)	95	97	96	98
Urinary excretion of oral dose (%)	77	14 to 23	30 to 35	71 to 80

PPIs = proton pump inhibitors.

Adapted with permission from Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc* 2000;40:53.

and lansoprazole (Prevacid), has been well established.<sup>2</sup> The safety profiles of the newer agents, rabeprazole and pantoprazole, appear to be similar to those of the older agents.<sup>2,5,7</sup> PPIs are only contraindicated if the patient has a known history of hypersensitivity to them, and they should be used with caution in patients with severe hepatic disease. Omeprazole is a pregnancy category C agent; the others are pregnancy category B medications. PPIs are not recommended for use in breastfeeding mothers.<sup>8-12</sup>

### Drug Interactions

PPIs cause significant increases in gastric pH, which may alter the absorption of weak acids or bases. They may inhibit the absorption of drugs such as griseofulvin (Grisactin), ketoconazole (Nizoral), itraconazole (Sporanox), iron salts, vitamin B<sub>12</sub>, cefpodoxime (Vantin), and enoxacin (Penetrex), many of which are weak bases and require acid for absorption.<sup>2,5,6,13</sup> Coadministration with these agents should be approached cautiously because it may result in clinical treatment failure.<sup>2</sup> PPIs are metabolized to varying degrees

by the hepatic cytochrome P450 enzymatic system and may alter drug metabolism by induction or inhibition of the cytochrome P enzymes.<sup>2,5</sup> This is an important consideration in patients taking medications with a narrow therapeutic window, such as diazepam (Valium), phenytoin (Dilantin), and warfarin (Coumadin). Omeprazole has the greatest potential for altering cytochrome P activity; the other PPIs are less likely to cause clinically significant drug interactions with these agents.<sup>5,13</sup> Table 2<sup>5</sup> illustrates the effects of PPIs on several medications.

### PPIs in Acid-Peptic Diseases

#### GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) can be diagnosed on the basis of the history alone in patients presenting with typical symptoms of heartburn, regurgitation, or both, especially after meals. These symptoms may be exacerbated by recumbency or bending, and relieved by antacids. It is appropriate to empirically treat patients with classic GERD symptoms with lifestyle modification and patient-directed antacid or acid suppres-

sion therapy.<sup>14</sup> PPIs are extremely effective acid suppressants, and it is likely that patients with GERD will respond to them. Physicians generally may assume that patients with typical symptoms who respond to PPI therapy have GERD.<sup>14,15</sup>

There is some debate about how to initiate treatment for GERD. There are two common approaches, but neither has been proved superior. It is left to the treating physician to determine which approach is most appropriate. Step-up therapy starts with over-the-counter or standard-dosage H<sub>2</sub> blockers and titrates to symptom control. Step-down therapy starts with once- or twice-daily PPI therapy and decreases the dosage or changes to the lowest form of acid suppression that will control the patient's symptoms.<sup>14</sup> In considering which approach would be best for a patient, the

*It is appropriate to empirically treat patients with symptoms of classic gastroesophageal reflux disease with lifestyle modification and acid suppression therapy.*

physician should consider that PPIs have been shown to be more effective and quicker to eliminate symptoms and heal esophagitis than H<sub>2</sub> blockers.

Regardless of treatment, certain patients with long-term symptoms are at increased risk for the development of Barrett's esophagus. There is no evidence that acid suppression therapy with PPIs causes regression of Barrett's esophagus or prevents progression to adenocarcinoma of the esophagus.<sup>2,14</sup> Thus, the duration of symptoms, rather than the

**TABLE 2**  
**Effects of PPIs When Coadministered with Other Drugs**

<i>Drug</i>	<i>Omeprazole (Prilosec)</i>	<i>Lansoprazole (Prevacid)</i>	<i>Pantoprazole (Protonix)</i>	<i>Rabeprazole (Aciphex)</i>
Carbamazepine (Tegretol)	↓ Metabolism	Unknown	None	Unknown
Clarithromycin (Biaxin)	*	None	Unknown	Unknown
Diazepam (Valium)	↓ Metabolism	None	None	None
Digoxin	↑ Absorption	Unknown	↑ Absorption	↑ Absorption
Ketoconazole (Nizoral)	↓ Absorption	↓ Absorption	Unknown	↓ Absorption
Methotrexate	↓ Renal excretion	Unknown	Unknown	Unknown
Nifedipine (Procardia)	↑ Absorption	Unknown	↑ Absorption	Unknown
Oral contraceptives	None	None	None	Unknown
Phenytoin (Dilantin)	↓ Metabolism	None	None	None
Warfarin (Coumadin)	↓ Metabolism	None	None	None
Theophylline	None	↑ Metabolism	None	None

*PPIs = proton pump inhibitors; ↓ = decreased; ↑ = increased.*

*\*—Omeprazole increases gastric mucous concentration of clarithromycin, and clarithromycin inhibits cytochrome P450 metabolism of omeprazole.*

*Information from Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. J Am Pharm Assoc 2000;40:52-62, and Reilly JP. Safety profile of the proton-pump inhibitors. Am J Health Syst Pharm 1999;56(23 suppl 4):S11-7.*

symptom complex or type of treatment, is a more important consideration in determining the need for an endoscopic evaluation to rule out Barrett's esophagus.<sup>14,15</sup> While most patients with typical symptoms of GERD responsive to empiric therapy do not require endoscopy, patient whose symptoms do not respond to PPI therapy most likely do not have GERD, and further evaluation of their symptoms is needed.<sup>14,15</sup>

#### PEPTIC ULCERS

Peptic ulcers usually occur in patients with normal acid secretion and gastroduodenal mucosal defenses disrupted because of *Helicobacter pylori* infection or therapy with non-steroidal anti-inflammatory drugs (NSAIDs). Studies of PPIs have demonstrated superior healing rates, shorter healing time, and faster symptom relief than are obtained with H<sub>2</sub> blockers in these patients.<sup>2-4</sup> PPIs have been shown to heal peptic ulcers that may be refractory even to high-dose H<sub>2</sub>-receptor blockers, and they also exhibit antimicrobial activity against *H. pylori* in vitro. While the mechanism of this antimicrobial activity is unclear, it is probably related to inhibition of the urease enzyme produced by *H. pylori*.

PPIs only suppress *H. pylori* in vivo, and antibiotics alone are ineffective in eradicating *H. pylori*. A combination of adequate acid suppression and antibiotic therapy is necessary for the successful eradication of *H. pylori*.<sup>2-4</sup> The recurrence rate of peptic ulcers after one

year is less than 10 percent when the combination of a PPI and antibiotics is used for *H. pylori* eradication.<sup>2,6</sup>

#### NSAID-INDUCED GASTROPATHY

NSAIDs cause peptic ulcers by inhibiting prostaglandin synthesis and weakening gastroduodenal mucosal defenses. Uncomplicated ulcers usually heal after discontinuation of NSAIDs and treatment with standard dosages of PPIs, H<sub>2</sub> blockers, or sucralfate (Carafate). PPIs are the treatment of choice for large or complicated ulcers,<sup>2,16</sup> and they may also be used for prevention of NSAID-induced ulcers. Omeprazole at a dosage of 20 mg daily has been shown to be better tolerated and associated with a lower relapse rate than misoprostol (Cytotec) at a dosage of 200 mcg twice daily.<sup>2,16,17</sup> Omeprazole and misoprostol appear to be equally effective in preventing NSAID-induced ulcers.<sup>16</sup>

#### Dosage and Administration

PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release gelatin capsules containing enteric-coated granules (omeprazole and lansoprazole) or in delayed-release enteric-coated tablets (rabeprazole and pantoprazole).<sup>2,8-11</sup> Omeprazole is supplied in doses of 10, 20, and 40 mg, and lansoprazole is supplied in doses of 15 and 30 mg. Both of these agents should be taken 30 minutes before meals, and their capsules should not be opened, chewed, or crushed, but should be swallowed whole.

Other methods of administering omeprazole, lansoprazole,<sup>2,8,9</sup> or esomeprazole<sup>12</sup> have been recommended for patients who are unable to swallow intact capsules. The capsules may be opened and the granules sprinkled over a tablespoon of applesauce, pudding, yogurt, or cottage cheese; the food must be swallowed immediately without stirring, crushing, or chewing. In patients with nasogastric or gastrostomy tubes, the granules in one capsule may be mixed with 40 mL of apple juice and injected through the tube,

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which should be flushed with additional juice to clear the tube.

Rabeprazole is supplied in one dose of 20 mg, and pantoprazole (Protonix) is supplied in one dose of 40 mg. Both agents must be swallowed whole without crushing, chewing, or splitting. Rabeprazole should be taken after meals, but pantoprazole may be taken without regard to meals. Antacids may be administered concomitantly with all PPIs. Dosage adjustments for PPIs are not necessary in elderly patients or those with renal failure or mild hepatic impairment. Lansoprazole, rabeprazole, and pantoprazole should be used with caution in patients with severe hepatic impairment.<sup>2,8-12</sup>

The FDA has not approved pantoprazole for maintenance therapy because safety has not been established beyond 16 weeks. At this time, pantoprazole is indicated by the FDA only for the treatment of erosive esophagitis in a dosage of 40 mg daily for eight to 16 weeks.<sup>11</sup> It is the only PPI available for intravenous administration and has recently been approved by the FDA for the short-term intravenous treatment (seven to 10 days) of GERD in hospital inpatients who are unable to take an oral PPI. The intravenous dosage is the same as the oral dosage (40 mg) and should be administered slowly over two to 15 minutes.<sup>1,2,18</sup>

Esomeprazole is the *s*-isomer of omeprazole. It is more bioavailable than omeprazole as the result of a lesser first-pass effect and slower plasma clearance. Esomeprazole in dosages of 20 and 40 mg produces higher 24-hour intragastric pH levels than omeprazole, thus possibly resulting in superior acid control. The incidence and types of adverse effects appear to be similar to those of omeprazole.<sup>19</sup>

Esomeprazole is supplied as delayed-release capsules containing enteric-coated pellets and is available in doses of 20 and 40 mg. It should be taken one hour before meals, and dosage adjustment is not necessary in elderly patients or those with mild to moderate hepatic impairment. Daily dosages should not exceed 20 mg in patients with severe hepatic impairment.

*Proton pump inhibitors may be more cost effective than H<sub>2</sub> blockers because of their less frequent dosing requirements and shorter duration of required therapy.*

Esomeprazole is indicated for the short-term (four to eight weeks) treatment and healing of erosive esophagitis. If needed, an additional four to eight weeks of therapy may be considered. It is also indicated for maintenance therapy of erosive esophagitis; however, studies do not extend beyond six months of use. Esomeprazole, used as part of triple therapy, is indicated for the eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence.<sup>12</sup> Table 3<sup>2,6,8-10</sup> compares indications and dosages of omeprazole, lansoprazole, and rabeprazole.

### Recommendations

Although H<sub>2</sub> blockers are less expensive than PPIs, PPIs provide superior acid suppression, healing rates and symptom relief. Therefore, PPIs may be more cost-effective than H<sub>2</sub> blockers, especially in patients with more severe acid-peptic disorders, because of their lower and less frequent dosing requirements and their comparatively shorter duration of required therapy.<sup>20</sup> When deciding which PPI to use, physicians should consider the patient's age, medications, and diagnosis, as well as the expense of therapy.

All five PPIs appear to have similar efficacy in the treatment of various acid-peptic disorders. The newer agents, rabeprazole and pantoprazole, seem to have fewer drug interactions. This is a particularly important consideration in older patients who are already taking several other medications. While the average wholesale prices of all agents in this class are similar, pantoprazole is the least expensive.

Some controversy remains regarding the need to endoscopically evaluate patients before prescribing PPIs. It would be prudent

TABLE 3

## Indications and Recommended Dosages for Omeprazole, Lansoprazole, and Rabeprazole

Indication	Omeprazole (Prilosec)		Lansoprazole (Prevacid)	
	Dosage	Duration of treatment	Dosage	Duration of treatment
Short-term treatment of active duodenal ulcer	20 mg daily	4 weeks; another 4 weeks may be required	15 mg daily	4 weeks
<i>Helicobacter pylori</i> eradication for reduction of duodenal ulcer recurrence	Triple therapy: omeprazole, 20 mg, clarithromycin, 500 mg, and amoxicillin, 1,000 mg, each taken twice daily Dual therapy: omeprazole, 40 mg daily, and clarithromycin, 500 mg, each three times daily	Triple therapy: 10 days, plus 18 days of omeprazole therapy if an ulcer is present at initiation of treatment Dual therapy: 14 days, plus 14 days of omeprazole therapy at 20 mg daily if an ulcer is present at initiation of treatment	Triple therapy: lansoprazole, 30 mg, amoxicillin, 1,000 mg, and clarithromycin, 500 mg, each taken twice daily Dual therapy: lansoprazole, 30 mg, and amoxicillin, 1,000 mg, each taken three times daily	Triple therapy: 10 to 14 days Dual therapy: 14 days
Maintenance therapy for healed duodenal ulcer	NA	NA	15 mg daily	NA
Short-term treatment of gastric ulcer	40 mg daily	4 to 8 weeks	30 mg daily	Up to 8 weeks
Short-term symptomatic gastroesophageal reflux disease	20 mg daily	Up to 4 weeks	15 mg daily	8 weeks
Short-term erosive esophagitis	20 mg daily	4 to 8 weeks	30 mg daily	8 weeks; another 8 weeks of treatment may be required if not healed
Maintenance therapy of erosive esophagitis	20 mg daily	NA	15 mg daily	NA
Pathologic hypersecretory conditions	Dosages vary; recommended starting dosage is 60 mg daily; dosages of 120 mg three times daily may be needed; dosages of more than 80 mg daily should be divided	Treatment for several years may be required	Dosages vary; usual starting dosage is 60 mg daily, up to 90 mg twice daily; dosages of more than 120 mg daily should be divided	Treatment for years may be required

NA = not available.

Information from references 2, 6, and 8 through 10.

<i>Rabeprazole (Aciphex)</i>	
<i>Dosage</i>	<i>Duration of treatment</i>
20 mg daily	Up to 4 weeks; most will heal in this period; some patients may require additional therapy
NA	NA
NA	NA
NA	NA
NA	NA
20 mg daily	4 to 8 weeks; if not healed after 8 weeks, another 8 weeks of treatment may be considered
20 mg daily	NA
Dosages vary; usual starting dosage is 60 mg daily, and dosages of 60 mg twice daily may be required	Treatment for several years may be required

to consider endoscopic evaluation before initiating PPI therapy in patients 45 years or older and in those with atypical symptoms because pre-endoscopy treatment with a PPI could mask gastric cancer. While some authorities recommend that the *H. pylori* status of all patients requiring long-term PPI therapy be determined and that those who are positive for *H. pylori* receive appropriate treatment to eradicate the infection, the FDA's gastrointestinal drug advisory committee has issued assurances regarding the absence of the risk of atrophic gastritis and gastric carcinoma in these patients.<sup>6,21-24</sup> Esomeprazole may have increased bioavailability when compared with omeprazole, but otherwise it appears to be similar; omeprazole will soon be available in generic form.

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