A Critical Evaluation of Proton Pump Inhibitors in the Treatment of Gastroesophageal Reflux Disease

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Abstract

Proton pump inhibitors (PPIs) are the drugs of choice for treating gastroesophageal reflux disease (GERD). Their superiority to histamine$_2$ receptor antagonists (H_2RAs), cisapride, and sucralfate is directly related to their potent and prolonged suppression of gastric acid. The PPIs provide the most rapid relief of GERD symptoms and esophageal healing when compared with standard- or high-dose H_2RAs or cisapride. Their superiority over H_2RAs has also been demonstrated when used in maintaining esophageal healing and symptom relief. The cost effectiveness of standard-dose PPIs in the treatment of GERD has been well documented. High-dose PPI therapy may benefit patients with atypical GERD symptoms and may also be cost effective. Four PPIs are available in the United States: omeprazole, lansoprazole, rabeprazole, and pantoprazole. All 4 PPIs, when used in recommended dosages, are very effective for the acute and chronic treatment of GERD and demonstrate similar short- and long-term safety profiles. Subtle differences appear to exist, some of which are based on data obtained in vitro or from healthy volunteer studies and others on trends or relatively minor differences observed in selective clinical trials. In most cases, experience has not yet confirmed the clinical importance of these potential differences. The selection of a preferred PPI for a hospital or managed care formulary will most likely be based on the acquisition cost of the drug.

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The discovery of a new class of drugs, the proton pump inhibitors (PPIs), has dramatically influenced the treatment of acid-related diseases. The superiority of the PPIs to the histamine$_2$ receptor antagonists (H_2RAs), cisapride, and sucralfate in treating gastroesophageal reflux disease (GERD) is directly related to their potent and prolonged suppression of gastric acid. Treatment targeted at decreasing acid secretion and controlling the acidity of the refluxate is essential for symptom relief, esophageal healing, and maintenance of esophageal healing. Four PPIs are available in the United States: omeprazole, lansoprazole, rabeprazole, and pantoprazole.

This article provides a critical review of the PPIs used to treat GERD. Emphasis is placed on the comparative pharmacology, pharmacokinetics, clinical efficacy, and safety of omeprazole, lansoprazole, rabeprazole, and pantoprazole when used to relieve GERD symptoms, heal the esophagus, and prevent relapse.

GERD

Gastroesophageal reflux disease is a chronic illness. Symptomatic recurrence occurs within 6 months in as many as 80% of patients with healed esophagitis when drug treatment is discontinued or the drug dosage is reduced.[1] Although its pathogenesis is multifactorial, acidity of the refluxate

Any discussions of off-label uses are identified by an asterisk within the text.

is central to the development of symptoms, esophageal mucosal damage, complications, and recurrence.[1,2] Typical symptoms of GERD include heartburn, regurgitation, or dysphagia and atypical symptoms such as nocturnal choking, coughing, chronic hoarseness, chest pain, nonseasonal asthma, and dental erosions. Heartburn, which is the most common symptom, is not life-threatening but can be associated with esophageal inflammation, erosions, ulceration, and complications such as esophageal strictures.[1] Older age (ie, older than 60 years of age) contributes to GERD frequency and severity.[3,4] Long-standing symptomatic GERD is a risk factor for Barrett's esophagus and esophageal adenocarcinoma.[1,5] The high prevalence and chronic discomfort of heartburn, which may or may not be associated with esophagitis or related complications, decreases the patient's quality of life, increases the need for physician visits and hospitalization, and is costly to society.[6]

Drug Therapy

The management of GERD should be individualized and directed at relieving symptoms, healing esophagitis, preventing symptomatic recurrence, and increasing health-related quality of life, cost effectively. Dietary and lifestyle modifications are the cornerstone of GERD therapy, even though the evidence to support these strategies is either marginal or lacking.[7,8] Antacids and alginic acid are useful in treating patients with mild, infrequent heartburn. Nonprescription H_2RAs (cimetidine, ranitidine, famotidine, and nizatidine) have a slower therapeutic onset than do antacids, but they also have a longer duration of action.[9] The H_2RAs, when given in prescription dosages divided throughout the day (eg, ranitidine, 150 mg twice daily), effectively relieve mild-to-moderate GERD symptoms.[9,10] High-dose H_2RAs (eg, ranitidine, 150 mg 4 times a day) and a longer treatment period (8 to 12 weeks) are usually required for patients with more severe symptoms and esophagitis.[9,10] The efficacy of cisapride in most patients with GERD is similar to that of standard-dose H_2RAs.[10] Combining an H_2RA with cisapride provides 2 different mechanisms of drug action but only modestly increases efficacy over that of H_2RA or cisapride when used as single agents.[10] Because sucralfate has no clinically important effect on gastric acid, its efficacy in relieving symptoms and healing esophagitis is inferior to that of the antisecretory drugs. Therefore, it should not be used in treating most patients with GERD.

The PPIs provide the most rapid relief of GERD symptoms and esophageal healing in the highest percentage of patients when compared with the effects of standard- or high-dose H_2RAs or cisapride.[7,9-15] Most GERD patients will require long-term treatment to remain asymptomatic and sustain esophageal healing.[9,10] Long-term and continuous antisecretory therapy is effective and appropriate for many patients with GERD. Patients with moderate-to-severe symptoms or esophagitis, whose disease has been initially controlled with PPIs, frequently require PPI maintenance dosages similar to those used for initial esophageal healing. Increasing evidence indicates that high-dose PPI therapy benefits patients with atypical symptoms.[16-19] Thus, PPIs play an important and pivotal role in treating patients with GERD.

Pharmacologic Aspects of GERD Treatment

Gastric Antisecretory Effects. All 4 PPIs (omeprazole, lansoprazole, rabeprazole, and pantoprazole) are substituted benzimidazoles that noncompetitively inhibit H^+K^+-ATPase (the proton pump), which is the final stage in gastric acid secretion. After being absorbed from the proximal

small intestine, PPIs enter the canalicular lumen of the parietal cell where, at low pH values, they are protonated, trapped, concentrated, and activated by conversion to the sulfenamide.[11] The activated sulfenamide binds covalently to cysteine residues in a subunit of the actively secreting proton pump, thereby irreversibly inhibiting H^+K^+-ATPase and gastric acid secretion. Restoration of acid secretion by the parietal cell requires translocation of new proton pumps.[20]

Pantoprazole, the most stable PPI at moderately high pHs (eg, greater than 3.0), binds only to cysteine residues (813 and 822) that play a crucial role in inhibiting gastric acid.[11] In contrast, omeprazole, lansoprazole, and rabeprazole bind to additional cysteine residues that appear unrelated to their acid-inhibiting effects. Differences in binding may contribute to differences in efficacy or safety. However, the clinical importance of pantoprazole's selective binding to acid-inhibiting cysteine residues has yet to be determined. Rabeprazole undergoes activation over a greater pH range and converts to the sulfenamide more rapidly than do the other 3 PPIs.[20] However, rabeprazole's faster rate of gastric acid inhibition does not consistently or dramatically accelerate relief of GERD symptoms when compared with the effect of omeprazole.[21] In vitro data have shown that the binding of rabeprazole is partially reversible, but its clinical importance in vivo is unclear.[11]

All 4 PPIs inhibit basal and stimulated gastric acid secretion and dose-dependently increase the extent and duration of acid inhibition. Although lansoprazole (30 mg/day), rabeprazole (20 mg/day), and pantoprazole (40 mg/day) may have a somewhat longer duration of acid suppression (ie, intragastric pH greater than 3.0 is maintained over 24 hours) than omeprazole (20 mg/day), the individual antisecretory response to a PPI varies among patients and does not necessarily result in improved outcomes.[11] Thus, comparative gastric pH profiles derived from in vitro models and pH studies in healthy volunteers are of interest, but the superiority of one PPI to another in such studies does not necessarily translate into clinically important differences in the 4 agents used to treat most patients with GERD.

Pharmacokinetics. Orally administered omeprazole, lansoprazole, rabeprazole, and pantoprazole exhibit similar pharmacokinetics in healthy volunteers (Table 1) and in special patient populations (Table 2). The bioavailability of omeprazole is initially about 35% but increases to 60% with multiple daily dosing.[22] The PPIs' relatively prolonged pharmacodynamic action, when compared with their short pharmacokinetic half-life,

Table 1. Pharmacokinetics of Oral PPIs in Healthy Volunteers

Characteristic	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Bioavailability (%)	30-40	80-85	52	77
Time to peak plasma concentration (hr)	0.5-3.5	1.7	2.0-5.0	1.1-3.1
Plasma elimination half-life	0.5-1	1.3-1.7	1.0-2.0	1.0-1.9
Protein binding (%)	95	97	96	98
Urinary excretion of oral drug (%)	77	14-23	30-35	71-80
Secretion into breast milk	Yes	Yes	Yes	Yes
Pregnancy category*	C	B	B	B

*FDA-assigned pregnancy categories: B = animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; C = animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies on humans.

Source: Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc* 2000;40(1):52-62. Adapted with permission from the American Pharmaceutical Association, Copyright 2000.

reflects the sustained inactivation of the proton pump. All 4 PPIs are extensively metabolized by the hepatic cytochrome P 450 (CYP450) isoenzyme system to inactive or less-active metabolites that are eliminated primarily in the urine.[11,22,23] The principal isoenzymes involved in the metabolism of all 4 PPIs are CYP2C19, an isoform that exhibits polymorphism, and CYP3A4. The magnitude to which CYP2C19 contributes to the metabolism of the PPIs varies accordingly: omeprazole >pantoprazole >lansoprazole >rabeprazole.[24] Different CYP2C19 genotypes, which are characterized by several phenotypes (eg, extensive metabolizers or poor metabolizers), may influence PPI metabolism. The extent to which pharmacokinetic alterations among agents account for clinically important differences is being examined. A small portion of Caucasians (2% to 6%) and a higher portion of Asians (13% to 23%) have been identified as poor metabolizers of CYP2C19.[24] The pharmacokinetics of all 4 PPIs is substantially altered in the elderly and in patients with liver dysfunction (Table 2), but dosage reductions are usually unnecessary.[23] There are no important phamacokinetic changes in patients with renal dysfunction. Pantoprazole also undergoes conjugation in the liver.

Table 2. Pharmacokinetics of Oral PPIs in Special Patient Populations

Characteristic	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Elderly	↑ AUC ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$*
Renal dysfunction	No significant changes	No significant changes	No significant changes	No significant changes
Hepatic dysfunction	↑ AUC ↑ ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$	↑ AUC ↑ $t_{1/2}$

AUC = Area under the concentration/time curve; $t_{1/2}$ = elimination half-life.
*Changes were not substantial and may reflect differences in the age range of the populations studied.

Source: Swan SK, Hoyumpa AM, Merritt GJ. Review article: The pharmacokinetics of rabeprazole in health and disease. *Aliment Pharmacol Ther* 1999; (suppl3):11-17. Adapted with permission from Blackwell Science LTD.

Effects on Gastrin. All 4 PPIs cause a mild-to-modest dose-related increase in fasting serum gastrin (usually within the normal range), which usually returns to pretreatment levels within 1 week of discontinuing therapy.[11,25] Although some patients may develop enterochromaffin-like (ECL) hyperplasia secondary to prolonged hypergastrinemia, the effect is consistent for all 4 PPIs. To date, there have been no reports of patients who have developed a carcinoid tumor or dysplastic or neoplastic changes of the gastric mucosal ECL cells with any of the PPIs.

PPIs: Therapeutic Uses and Efficacy

Symptom Relief and Esophageal Healing. All 4 PPIs are highly effective in relieving GERD symptoms and in healing esophagitis. Numerous double-blind, placebo-controlled trials[9-14] have demonstrated the superiority of omeprazole, lansoprazole, rabeprazole, and pantoprazole over placebo, standard- and high-dose H_2RAs, and cisapride in reducing both the frequency and the severity of heartburn and in accelerating esophageal healing. Mean symptomatic relief and esophageal healing over 4 to 8 weeks are reported to occur in greater than 80% and 90% of patients, respectively.[10] In most double-blind trials in which lansoprazole (30 mg/day), rabeprazole (20 mg/day), or pantoprazole (40 mg/day) were compared with omeprazole (20 mg/day), esophageal healing rates at 4 and 8 weeks were similar.[9-14,21,26,27] Resolution of GERD symptoms was also comparable at most points in time. In several clinical trials in which the effect of lansoprazole (30 mg/day) was compared with

that of omeprazole (20 mg/day), more rapid relief of heartburn (by about 1 day) was noted during the first week of treatment with lansoprazole.[28,29] In a European trial[30] that compared lansoprazole with omeprazole in patients with moderate-to-severe esophagitis, rates of esophageal healing with lansoprazole (30 mg/day) were similar to those produced by omeprazole (40 mg/day).

The PPIs are the drugs of choice for patients with frequent daily GERD symptoms, moderate-to-severe GERD symptoms, and esophagitis. In most patients, the recommended dosages (Table 3) of omeprazole, lansoprazole, rabeprazole, and pantoprazole will relieve GERD symptoms within several days of treatment initiation and will heal the esophagus in 4 to 8 weeks. *Patients with continued symptoms or those who have more severe disease will require higher PPI dosages, more frequent administration, and longer treatment. *Combination therapy with a PPI and a prokinetic should be reserved for patients who do not respond to high-dose PPIs or for those with abnormal motility disorders.

Maintenance of Esophageal Healing and Symptom Relief. Long-term maintenance therapy is especially important in patients with GERD because of the high rates of recurrence associated with discontinuing drug treatment. Maintenance therapy also may prevent serious complications that may develop as a result of chronic exposure of the esophagus to gastric acid. When used in recommended dosages, the efficacy of the PPIs in maintaining esophageal healing and symptom relief is well established.[9-14,31] Their superiority over the H_2RAs has also been demonstrated.[9-14,32] In a GERD maintenance trial that compared omeprazole (20 mg/day), ranitidine (150 mg 3 times a day), cisapride (10 mg 3 times a day), ranitidine (150 mg 3 times a day) plus cisapride (10 mg/day), and omeprazole (20 mg/day) plus cisapride (10 mg/day), omeprazole was more effective than either ranitidine or cisapride when used alone.[32] The combination of omeprazole plus cisapride was more effective than ranitidine plus cisapride.

Most patients with moderate-to-severe symptoms, erosive esophagitis, or complicated GERD will require continuous maintenance therapy after acute treatment with a PPI. Reports indicate that long-term therapy with appropriate PPI maintenance doses can be effective in as many as 100% of GERD patients.[10] Frequently, the same PPI dosage used to relieve symptoms and heal the esophagus is required to maintain symptom relief and esophageal healing. Although the lowest effective maintenance dose of a drug should always be used, lowering the PPI dose or switching to an H_2RA or cisapride is often associated with symptomatic recurrence. The results of a recent European trial[33] indicate that pantoprazole 20 mg/day was at least as effective as 40 mg/day with respect to preventing symptomatic and endoscopic recurrence in patients with grade 2 and 3 esophagitis who were initially healed with either pantoprazole (40 mg/day) or

Table 3. Dosage Regimens of Oral PPIs Used to Treat GERD

Indication (Duration)	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Relief of GERD symptoms (4 wks)	20 mg	15 mg	20 mg*	20 mg*
Healing of erosive esophagitis (4 to 8 wks)	20-40 mg	30 mg	20 mg	40 mg
Maintenance of esophageal healing (1 yr)	20 mg	15–30 mg*	20 mg	20*-40 mg*

GERD = Gastroesophageal reflux disease.*Regimen not approved by the Food and Drug Administration.

omeprazole (20 mg/day). The effectiveness of a lower PPI maintenance dose, however, depends on a number factors, one of which is the initial severity of the disease. Different PPI dosage regimens (eg, every other day or weekend-only regimens) have been studied but are not as effective as daily maintenance therapy.[11,14]

Barrett's Esophagus. Barrett's esophagus (replacement of the normal epithelium in the esophagus with specialized columnar epithelium) is a premalignant condition that occurs secondary to long-standing GERD. The incidence of malignant transformation is approximately 1 per 100 patients.[1] Controversy exists about whether continuous gastric acid suppression with PPIs contributes to partial or complete regression of Barrett's epithelium.[34-36] A 5-year study of continuous acid suppression with omeprazole (40 mg/day) suggests that the treatment was partially beneficial, but none of the changes was assessed to determine whether the risk of malignancy was reduced as a result of therapy.[34] In contrast, other reports[35,36] suggest that PPI therapy does not result in a clinically meaningful regression of Barrett's esophagus. It is likely that other factors (eg, genetic, environmental, or absence of hiatal hernia) rather than potent acid suppression play a more important role in the regression of Barrett's esophagus.[35,36]

Atypical Symptoms. While GERD is associated with a variety of atypical symptoms, laryngitis is one of the most common.[16] *Treatment of suspected reflux laryngitis (hoarseness and sore throat) with PPIs has been shown to be effective, however, none of the trials to date has been placebo controlled.[16] Empiric therapy using high-dose PPIs (omeprazole, 20 mg twice daily; lansoprazole, 30 mg twice daily) for relatively long periods (3 to 6 months) appears necessary to heal laryngeal mucosa and for symptoms to resolve. In a prospective, double-blind, placebo-controlled trial to treat acid-related chronic cough, omeprazole (40 mg twice daily) was given in the morning and at bedtime for 12 weeks.[17] Approximately 35% of the patients studied responded to the omeprazole therapy. Possible reasons for treatment failure include the fact that the second dose of omeprazole was taken at bedtime rather than at the optimal time (before dinner).

The cost effectiveness of strategies to assess GERD as an exacerbating factor in asthma and noncardiac chest pain has also been evaluated.[18,19] When a cost-effectiveness analysis model was used to compare 11 diagnostic strategies for assessing the role that acid reflux plays in asthma, the most cost-effective diagnostic approach was that of initiating empiric therapy with omeprazole (20 mg/day) for 3 months followed by 24-hour esophageal pH testing in nonresponders.[18] Probabilities and costs were derived from the published literature; average costs, effectiveness, and cost effectiveness were calculated for each strategy. Because the results of this study are contrary to routine clinical practice (ie, initiate treatment with omeprazole [40 mg/day for 3 months], followed by pH testing in nonresponders), controlled clinical trials are required to confirm the response rate in patients with asthma. A second study[19] used a decision-analysis model to evaluate the economic effect of using omeprazole for the diagnosis of GERD in patients with noncardiac chest pain. Patients were randomized to receive either omeprazole (40 mg in the morning and 20 mg in the evening for 7 days) or placebo and were then "crossed over" after a washout period. The economic analysis revealed that omeprazole treatment saved $573 per average patient with noncardiac chest pain and resulted in a 59% reduction in the total number of diagnostic pro-

cedures.[19] This reduction in diagnostic tests was attributed to the high positive predictive value of the omeprazole test for GERD in this patient population.

PPI Use in Pregnancy

Heartburn is a common occurrence during pregnancy. Although most women have mild symptoms that are relieved with dietary and lifestyle modifications or by taking antacids or H_2RAs, a small percentage of women will require potent antisecretory therapy with a PPI. Women who are pregnant are not included in clinical trials for ethical reasons. Therefore, the safety of PPIs during pregnancy must be extrapolated primarily from animal studies, case reports, and human follow-up studies.[37-40] Women taking PPIs have given birth to healthy infants, but there have been several reports[39] of congenital malformations associated with having taken omeprazole that required termination of pregnancy. Because omeprazole has been available worldwide for about 15 years, much of what is known about the safety of taking PPIs during human pregnancy is based primarily on the study of omeprazole. Less is known about the safety of taking lansoprazole, pantoprazole, and rabeprazole during pregnancy.

A recent population-based cohort study[40] compared Danish women exposed to a PPI around the time of conception or during pregnancy with a control who had no exposure to prescribed medications. In the study, 38 women had been exposed to a PPI (omeprazole, 35; lansoprazole, 3) from 30 days before conception to the end of the 12th week of gestation and 51 had been exposed to a PPI at some time during pregnancy. This follow-up study found no substantially elevated risk of malformations, low birth weight, or preterm delivery in the offspring of women who had used PPIs during pregnancy. No stillbirths were recorded. However, that population-based study (as well as others that have been published previously) did not undergo statistical analysis to rule out possible elevated risks of malformations and low birth weight.

Until it is possible to rule out an association between PPIs and an increased risk of fetal malformations or preterm birth, the benefit of using a PPI during pregnancy must be weighed against the potential risk to the fetus.

Although the number of malformations and low birth weight offspring was small, exposure around conception or during the first trimester suggested a trend toward a higher risk of cardiac malformations. Until it is possible to rule out an association between PPIs and an increased risk of fetal malformations or preterm birth, the benefit of using a PPI during pregnancy must be weighed against the potential risk to the fetus.

Tolerability of PPIs

Overall PPIs are a well-tolerated class of drugs. Data from numerous clinical trials and clinical experience confirm the short-term adverse-effect profiles of omeprazole, lansoprazole, rabeprazole, and pantoprazole and their similarity to the H_2RAs.[11-13,26-29,41,42] The type and frequency of the most commonly reported adverse events—headache, diarrhea, nausea, and abdominal pain—are similar among the 4 agents.[11-13,26-29,41,42] The frequency of adverse effects of lansoprazole (30 mg/day; n = 422) and lansoprazole (15 mg/day; n = 218) when compared with those of omeprazole (20 mg/day; n = 431) or placebo (n = 213) in patients with erosive esophagitis were as follows[29]:

- Headache:
  Lansoprazole (30 mg) = 4.5%
  Lansoprazole (15 mg) = 4.1%
  Omeprazole (20 mg) = 3.9%
  Placebo = 3.3%
- Diarrhea
  Lansoprazole (30 mg) = 3.6%
  Lansoprazole (15 mg) = 4.1%
  Omeprazole (20 mg) = 3.9%
  Placebo = 3.3%
- Nausea
  Lansoprazole (30 mg) = 0.9%
  Lansoprazole (15 mg) = 3.7%
  Omeprazole (20 mg) = 0.7%
  Placebo = 0.5%

Freston et al[41] reported that diarrhea with lansoprazole was dose related and occurred in 7.4%, 4.2%, and 1.4% of patients taking 60 mg/day, 30 mg/day, or 15 mg/day, respectively. Dose-related diarrhea has also been observed in patients taking higher dosages (eg, 40 mg/day) of omeprazole. When rabeprazole and pantoprazole have been compared with omeprazole, the most common short-term adverse effects are similar to those reported with omeprazole, with diarrhea and headache sometimes occurring less frequently.[12,21,42] Data from long-term (1 year) studies with omeprazole (20 mg/day), lansoprazole (15 or 30 mg/day), rabeprazole (20 mg/day), and pantoprazole (20 or 40 mg/day) suggest a similar tolerability to that reported with their short-term use.[11-13,31,33,41,42] However, clinical experience worldwide favors the use of omeprazole, lansoprazole, and pantoprazole.

The Long-Term Safety of PPIs

Gastrin-Related Effects. All 4 PPIs, because of their potent acid-suppressant effects, are associated with a dose-related increase in fasting serum gastrin above pretreatment levels.[43,44] In most cases, the elevations are well within the normal range for fasting serum gastrin and return to baseline within 1 month of discontinuing the drug. PPI-induced hypergastrinemia has been linked to gastric ECL cell hyperplasia and possibly to gastric carcinoid tumors, gastric cancer, colonic polyps, and colorectal adenocarcinomas.[43,44] Although PPIs may promote changes in the gastric mucosa that lead to ECL cell hyperplasia, there is no evidence that ECL cell hyperplasia leads to ECL cell dysplasia, carcinoid tumors, or gastric cancer in humans. The original "black box" warning about omeprazole was included in the drug's product information because gastric neoplasms were reported in female rats.[44] However, the warning was eventually removed by the Food and Drug Administration (FDA) when long-term safety data about omeprazole and lansoprazole became available. There is inadequate evidence to presently support the association between PPIs and colonic polyps and colorectal adenocarcinoma. Most long-term safety data regarding PPIs have been derived from about 15 years of omeprazole use, but those data are supported by the long-term safety profiles of lansoprazole, pantoprazole, and rabeprazole. None of the 4 PPIs has been reported to cause gastric or colorectal cancer in humans.

Bacterial Overgrowth. Pharmacologic suppression of gastric acid by means of either an H_2RA or a PPI has been associated with increased bacterial counts and nitrosamine formation in the stomach.[43,44] Prolonged hypochlorhydria and resultant bacterial overgrowth are of theoretic concern because N-nitroso compounds are thought to be carcinogenic in animal models. However, a causal relationship between intragastric nitrosamines and gastric cancer in a patient taking either an H_2RA or a PPI has not been established in humans.[43,44]

Nutrient Absorption. Long-term studies of patients taking PPIs continuously suggest that the digestion of

protein and the absorption of calcium and iron are normal in those patients.[44] Additionally, most patients taking PPIs long term are unlikely to experience a vitamin B_{12} deficiency because of large body stores of vitamin B_{12}.[44] A slight decrease in B_{12} serum concentrations has been reported in a small number of patients on long-term (longer than 3 years) omeprazole therapy, although this is not a major clinical concern.

Helicobacter Pylori. The relationship between *Helicobacter pylori* and GERD is confusing and unresolved. Long-term PPI therapy in *H pylori*-positive GERD patients has been associated with rapidly progressive atrophic gastritis of the gastric body and with an increased risk of gastric cancer.[44-46] The results of one of the first studies[45] warning of this association have been questioned because of flaws in the study design. Other studies[46] have failed to show a similar association. In 1996, the FDA Gastrointestinal Drugs Advisory Panel concluded that there was inadequate evidence to suggest that the long-term use of PPIs in *H pylori*-positive patients contributes to the risk of gastric cancer.[47]

Drug Interactions

pH-Dependent. All 4 PPIs profoundly increase intragastric pH and have the potential to alter the rate or extent of absorption of pH-dependent drugs or dosage forms.[15,48,49] Increases in intragastric pH may predictably reduce the dissolution and absorption of weak bases (eg, ketoconazole, intraconazole, enoxacin, and cefpodoxime proxetil) and could potentially lead to therapeutic failure.[15,48,49] In contrast, increased intragastric pH may increase the absorption of digoxin and weak acids such as diazepam, aspirin, or furosemide.[15,48,49] The slight increases in absorption observed with these agents are unlikely to be clinically important.

Hepatic CYP450 Mediated. All 4 PPIs undergo hepatic metabolism by CYP450, 2C19, and 3A4 isoenzymes but differ in their potential to interact with specific CYP isoenzymes.[15,48-50]

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When studied in healthy volunteers, omeprazole reduced the clearance of selected drugs that are metabolized by hepatic CYP2C19, eg, phenytoin, diazepam, and R-warfarin (Table 4). Genetic polymorphism appears to be an important contributing factor because diazepam metabolism is inhibited by omeprazole in rapid metabolizers but not in slow metabolizers.[15,48] Pharmacokinetic interactions between omeprazole and R-warfarin (the less-active isomer) have not resulted in alterations in prothrombin time and thus are of questionable clinical importance.[15] Although the potential for omeprazole drug interactions exists with drugs metabolized by CYP2C19, the modest pharmacokinetic drug interactions observed in the small number of healthy volunteers studied must be balanced against the worldwide population of patients who during the past 15 years have safely taken drugs that might have interacted with omeprazole. Lansoprazole, pantoprazole, and rabeprazole do not appear to interact with drugs metabolized by CYP2C19 (Table 4), but there is less worldwide experience with rabeprazole.[15]

All 4 PPIs are metabolized to some extent by CYP3A4, but drug interactions involving that isoenzyme have not been reported.[15,48-50] It is possible that in poor metabolizers of

mephenytoin, CYP3A4 may become a dominant elimination pathway for PPIs. However, there is no evidence to substantiate that hypothesis. Omeprazole and lansoprazole induce CYP1A1 and CYP1A2, which are isoenzymes involved in the metabolism of caffeine and theophylline.[15] In one study,[50] lansoprazole increased the clearance of theophylline by about 10%, but the results of that study have not been duplicated. Omeprazole, pantoprazole, and rabeprazole do not interact with theophylline.[15,48-50] Theoretically, lansoprazole, rabeprazole, and pantopra-

Table 4. Effect of PPIs on the Hepatic Metabolism of Selected Drugs*

Drug	CYP Isoform	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Caffeine	1A2	Induce	Unknown	Unknown	None
Carbamazepine	3A4, 2C8?, 2C9?	Inhibit†	Unknown	Unknown	None
Cyclosporine	3A4	None	Unknown	Unknown	None‖
Diazepam	3A, 2C8, 2C19	Inhibit	None	None	None
Ethanol	2E1	None	Unknown	Unknown	None
Ibuprofen	2C9	Unknown	None	Unknown	Unknown
Lidocaine	3A4	None	Unknown	Unknown	Unknown
Metoprolol	2D6	None	Unknown	Unknown	None
Nifedipine	3A4, 3A5-7	None	Unknown	Unknown	None‖
Phenytoin	2C9/19	Inhibit	None	None	None
Prednisone	3A	None	None	Unknown	Unknown
Propranolol	2D6, others	None	None	Unknown	Unknown
Quinidine	3A4	None	Unknown	Unknown	Unknown
Theophylline	1A2, 2E1, 3A4	None	Induce‡	None	None
R-Warfarin	1A2, 3A4, 2C19	Inhibit§	None	None	None
S-Warfarin	2C9	None	None	None	None

? = possible interaction.
*Selected drugs metabolized by hepatic cytochrome P450 (CYP) isoforms in humans.
†Conflicting reports (reference 15) regarding the mechanism of this interaction as an increase in the AUC may be the result of hepatic inhibition of drug metabolism or increased drug absorption due to increased gastric pH.
‡One report (reference 50) notes an increase in theophylline clearance of 10% and a decrease in the AUC of 13%. The results of this report have not been duplicated.
§A small increase in R-warfarin serum concentration has been reported (reference 15).
‖Pantoprazole does not appear to interact with cyclosporin[51] or nifedipine.[52]

Source: Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc* 2000;40(1):52-62. Adapted with permission from the American Pharmaceutical Association, Copyright 2000.

zole have a lower potential for CYP-mediated drug interactions, but the absence of clinically important interactions with omeprazole given its widespread use must be placed in proper perspective.

Dosage and Administration

Formulations and Routes of Administration. All 4 PPIs are lipophilic weak bases and are unstable in gastric acid. Therefore, the oral drug is formulated as either a gelatin capsule containing enteric-coated granules (omeprazole or lansoprazole) or enteric-coated tablets (rabeprazole or pantoprazole). Chewing or crushing the granules or tablets may lead to inactivation of the PPI by the acidic contents of the stomach. Because none of the 4 PPIs is available in an oral liquid, various methods of administration have been suggested for patients unable to swallow the intact tablet or capsule. Omeprazole or lansoprazole granules may be removed from their capsule and administered in juice (eg, orange or apple juice) or sprinkled on soft foods, such as applesauce. When the granules are mixed with apple or orange juice, they may be administered through a nasogastric or gastrostomy tube.[15] Omeprazole or lansoprazole granules may also be administered through a nasogastric tube when mixed with a 8.4% sodium bicarbonate solution.[15,53] However, only lansoprazole includes instructions in its product information on the administration of the intact granules in juice, on soft foods, or through tubes. Rabeprazole or pantoprazole tablets should not be crushed and thus cannot be used for children or adults who cannot swallow the intact tablet or for patients with feeding tubes. Pantoprazole, if the FDA approves it in parenteral form, will be the first PPI available in this form and may be useful in hospitalized patients unable to take oral medications.

Dosage, Frequency, and Administration Times. The majority of patients with GERD will achieve favorable results when a PPI is taken once a day in its recommended dosage and for the appropriate length of time. *Patients with more severe or complicated disease often require higher dosages and twice-daily administration (eg, omeprazole [20 mg twice daily] or lansoprazole [30 mg twice daily]). *Higher-than-usual PPI dosages and a longer treatment duration are necessary in patients with atypical GERD symptoms (see *Atypical Symptoms*). The optimal time to take a PPI is about 5 to 30 minutes before a meal. This enables the PPI to act on the actively secreting parietal cell so that acid inhibition is maximized. When twice-daily dosing is necessary, patients should be advised to take their PPI before breakfast and before dinner. The clinician should counsel the patient to be sure to eat an adequate meal so that acid secretion is stimulated.

The majority of patients with GERD will achieve favorable results when a PPI is taken once a day in its recommended dosage and for the appropriate length of time.

Combination Therapy

Little evidence exists to support the use of combination therapy for patients with symptomatic GERD. The PPI dosage should be optimized first before an additional medication is added. *The combined use of a PPI and cisapride may be warranted in patients with GERD who have altered motility disorders or who are unresponsive to maximal PPI dosages.[10] However, any possible benefit of cis-

apride must be weighed against the potential of this agent to precipitate (occasionally fatal) cardiac arrhythmias. *The addition of an H_2RA (eg, 300 mg at bedtime) to a twice-daily PPI regimen in patients with nocturnal breakthrough is controversial, and its superiority remains unproven in GERD patients.[54,55] Increasing the daily PPI dosage and ensuring that the second dose is taken before dinner may control nocturnal breakthrough and avoid the use of an H_2RA. PPIs and other antisecretory agents, including H_2RAs, misoprostol, and octreotide, should not be taken simultaneously. Concomitant administration will diminish or abolish the effectiveness of the PPI.

Pharmacoeconomic Considerations

An important goal of pharmacologic therapy is to treat GERD patients with the most cost-effective drug regimen. The H_2RAs are most economical when they are used to relieve mild, infrequent GERD symptoms.[56] In patients with moderate-to-severe symptoms and esophagitis, a standard-dose PPI is more efficacious and cost effective than a high-dose H_2RA.[57] The cost effectiveness of maintenance therapy with either an H_2RA or PPI depends primarily on the severity of the disease.[56] Health-related quality of life, which is an important therapeutic outcome, can be improved with PPI treatment in patients with symptomatic erosive esophagitis.[6,59]

Histamine$_2$ receptor antagonists are often used as initial therapy when treating GERD because their acquisition costs are significantly less than those of the PPIs. Although this strategy may appear to be an important cost-saving measure, the reduced efficacy of the H_2RAs (when compared with that of PPIs) in treating patients with frequent daily GERD symptoms or moderate-to-severe GERD often leads to prolonged or suboptimal treatment, higher H_2RA dosages, relapse, increased number of visits to a physician and hospitalizations, and an impaired health-related quality of life for patients.[58,59] Additionally, the initial use of a PPI (the omeprazole test) instead of an H_2RA appears to increase diagnostic accuracy and cost savings.[58,60] Higher PPI acquisition costs are offset in patients with frequent daily symptoms or moderate-to-severe disease because of the greater efficacy of the PPIs which, in turn, reduces the number of necessary diagnostic procedures, visits to physicians, and GERD-related complications.

Conclusion

Gastric acid suppression is the cornerstone of effective management in patients with GERD. Greater and more prolonged control of gastric acid is associated with a more rapid resolution of symptoms, improved symptom relief, and an accelerated rate of esophageal healing. The H_2RAs are effective for patients with mild, infrequent GERD symptoms. The PPIs, however, because of their profound effect on gastric acid secretion, have revolutionized the treatment of GERD in patients with frequent daily symptoms, moderate-to-severe symptoms, and esophagitis. These agents hasten symptom relief and esophageal healing, provide a longer duration of action, and when used as maintenance therapy, they minimize disease recurrence. The cost effectiveness of standard-dose PPIs in the treatment of GERD has been well documented. Patients with atypical GERD symptoms can now be diagnosed by means of empiric high-dose PPI treatment, an approach that also may be cost effective.

All 4 PPIs in the class, omeprazole, lansoprazole, rabeprazole, and pantoprazole, when used in recommended dosages, are very effective for the acute and chronic treatment of GERD and demonstrate similar short- and long-term safety profiles. Subtle differences appear to exist, some of

which are based on data obtained in vitro or from healthy volunteer studies and others on trends or relatively minor differences observed in select clinical trials. In most cases, experience has not yet confirmed the clinical importance of those potential differences. Therefore, the selection of a preferred PPI for a hospital or managed care formulary will most likely be based on the acquisition cost of the drug.

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