Review Article

CME

Proton Pump Inhibitors: The Good, the Bad, and the Unwanted

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Abstract: Proton pump inhibitors (PPIs) are one of the most commonly prescribed classes of medications in the United States. By inhibiting gastric H^+/K^+ adenosine triphosphatase via covalent binding to the cysteine residues of the proton pump, they provide the most potent acid suppression available. Long-term PPI use accounts for the majority of total PPI use. Absolute indications include peptic ulcer disease, chronic nonsteroidal anti-inflammatory drugs use, treatment of *Helicobacter pylori*, and erosive esophagitis. Although PPIs are generally considered safe, numerous adverse effects, particularly associated with long-term use have been reported. Many patients receiving chronic PPI therapy do not have clear indications for their use, prompting consideration for reduction or discontinuation of their use. This article reviews the indications for PPI use, the adverse effects/risks involved with their use, and conditions in which their use is controversial.

Key Words: *Clostrdium difficile*, *Helicobacter pylori*, clopidogrel, proton pump inhibitors, reflux

Proton pump inhibitors (PPIs) are among the most widely sold drugs in the world, and in the United States, they are the third most widely sold drug class, with annual sales of $13.9 billion.[1] Overall, they are considered safe and effective. PPIs are a class of medication that act on the H^+/K^+ pump along the basolateral membrane of the parietal cell. They accumulate and activate in an acid environment at the secretory canalicular surface of the parietal cell. Here, they bind irreversibly to H^+/K^+ adenosine triphosphatase, inhibiting acid production of the bound parietal cell in approximately 70% of active pumps.[2,3] Protonation forms irreversible disulfide bonds with cysteine residues in the proton pump, two of which are most important, CYS813 and CYS822.[4] The need to achieve acid exposure in the parietal cell but not the stomach is why PPIs should be taken 20 minutes before eating breakfast.[4]

PPIs differ in their routes of excretion, peak plasma levels, and half-lives (Table). They have short half-lives, typically 1 hour, but may last up to 24 hours because of the necessity of new pump synthesis for acid secretion. All PPIs are eliminated via hepatic P-450 CYP2C19, with CYP3A4 also playing a role.[5] Lansoprazole, pantoprazole, and dexlansoprazole have the greatest bioavailability and achieve the highest plasma levels. Rabeprazole is the most acid-labile PPI and therefore the most potent, whereas pantoprazole is the least reactive and therefore the least potent.[5–8] Numerous studies have evaluated whether these differences are of clinical significance and would therefore justify choosing one PPI over another. To date, no comparative trial has established the superiority of a single PPI. This review addresses the indications for PPI use, adverse effects, and their overuse.

Indications

Evidence supporting the use of PPIs in peptic ulcer disease (PUD) includes its ability to offer suppression of acid secretion, ulcer healing, and symptom relief that is superior to suppression that is associated with other antisecretory therapies, and has led to their role as the mainstay of therapy (level of evidence A).[9] Much of the morbidity and mortality arising from PUD arises from rebleeding. Patients with bleeding peptic ulcers who are treated with a PPI have demonstrated a decrease in the need for transfusions or surgery and a reduction in length

Key Points

- Proton pump inhibitors (PPIs) are highly effective when prescribed for peptic ulcer disease.
- Adverse effects of PPI use warrant consideration both before initiating treatment and when continuing therapy.
- PPIs are often overused in clinical scenarios, including nonerosive reflux disease and nonulcer dyspepsia.

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Table. Comparison of proton pump inhibitors

Agent	Half-life, h	Metabolism	Bioavailability, %	Elimination
Omeprazole	0.5–1	Hepatic	40–50	Renal
Lansoprazole	1.5	Hepatic	80–90	Renal/fecal
Rabeprazole	1–2	Hepatic; more CYP3A4	52	Renal
Pantoprazole	1	Hepatic; less CYP2C19	77	Renal
Esomeprazole	1–1.4	Hepatic	89	Renal
Dexlansoprazole	1–2	Hepatic	50–60	Renal/fecal

of hospital stay, although no effect has been noted for all-cause mortality.[10] PPIs given for 4 weeks for a duodenal ulcer and 8 weeks for a gastric ulcer are associated with a 100% and an 80% rate of healing, respectively. Maintenance therapy with PPIs prevents the recurrence of ulcer formation in patients with a history of recurrent ulcers, negative *Helicobacter pylori*, and large ulcers.[11] Such patients are considered high risk.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to increase the risk of dyspepsia and peptic ulcers, with up to 25% of long-term NSAID users developing ulcer disease.[12] According to the 2009 American College of Gastroenterology guidelines, patients taking daily NSAIDs long term should be considered for preventive therapy with daily PPIs.[13] Several randomized studies have shown the superiority of PPIs in both healing of NSAID-associated ulcers and preventing recurrence of these ulcers.[14,15] Patients who have experienced a gastric ulcer bleed and use of both a cyclooxygenase-2 inhibitor and a PPI have no recurrent events at all.[16] In the setting of active ulcer disease, an appropriate course of PPI therapy (4 weeks for duodenal ulcers and 8 weeks for gastric ulcers) should be used in addition to discontinuing NSAIDs.

H pylori has been associated with both gastric and duodenal ulcers. To facilitate healing and to decrease the risk of ulcer recurrence, *H pylori* should be eradicated (level of evidence A). Successful eradication reduces the need for long-term antisecretory therapy and additional surgery (level of evidence C).[17] Eradication therapy leads to improved ulcer healing and a dramatic decrease in ulcer recurrence from 50% to 8% for duodenal ulcers.[18] Most eradication regimens are 70% to 90% effective in practice, limited mainly by antibiotic resistance and patient adherence to the regimen. Triple therapy (PPI + two antibiotics) historically has been preferred over quadruple therapy (PPI + bismuth + two antibiotics) because of relative simplicity. With regard to maintenance, no guidelines exist for when to discontinue PPI therapy after *H pylori* eradication.

Erosive esophagitis (EE) is a common complication in gastroesophageal reflux disease (GERD), accounting for approximately 20% to 40% of cases. It is widely recognized that patients with EE develop complications (eg, bleeding, strictures, Barrett esophagus). PPIs provide healing of erosive esophagitis and relief of symptoms in patients with GERD, with intragastric pH >4.0 positively correlating with healing of EE.[19,20] Studies have shown that PPIs healed EE in at least 84% of patients with daily use, with 12-month maintenance success rates ranging from 78% to 82% with daily use.

Use of PPIs in Barrett esophagus can provide symptomatic benefits with regard to heartburn relief, prevention of stricture formation, and more effective and faster healing of esophagitis and esophageal ulcers than H2 antagonists.[21] Although controversial, PPI use for chemoprophylaxis in Barrett esophagus has been recommended by some authorities based on two clinical trials showing partial regression of intestinal metaplasia.[22,23] Despite this, the indication for medical therapy in Barrett esophagus is the same as that for GERD, which is control of symptoms and healing of esophageal mucosa. Further studies are needed to address whether abolishing acid completely with high-dose PPIs will decrease the risk of esophageal adenocarcinoma, be cost effective, and warrant the risk of adverse effects.

Adverse Effects

PPI use is not, however, without shortcomings. Primary adverse events, typically on the order of 1% to 5%, include headache, diarrhea, constipation, nausea, and rash. Such adverse effects are largely class associated, with little variation among individual PPIs. No studies have been performed comparing different PPIs with regard to primary adverse effects. Secondary adverse effects associated with long-term use include osteoporosis, increased risk of enteric infections, altered metabolism of other medications, and formation of gastric polyps/carcinoid.

Significant attention has been given to the potential interaction between clopidogrel and PPIs because clopidogrel requires biotransformation via CYP2C19 to become active, which is the same pathway through which PPIs are primarily metabolized. Four studies have yielded conflicting results regarding the interaction, the first of which found a hazard ratio of 1.29 for recurrent myocardial events associated with the use of both a PPI plus clopidogrel.[24] A second study noticed a trend toward increased cardiovascular events, recognizing that such events were likely secondary to a channeling bias because PPI exposure was likely simply a reflection of more severe cardiovascular disease, rather than secondary to PPI exposure.[25] A third study was then performed, using four times the standard dose of omeprazole (80 mg) and noting a significant interaction, while noting less of an interaction with pantoprazole.[26] The

final study did not reveal any interaction at all.[27] Thus, guidelines suggest that if there are indications for use of PPI and clopidogrel, then there are no cardiovascular endpoints to justify withholding any PPI.

PPI use leads to diminished acid secretion, diminished somatostatin release, and thus increased G-cell release of gastrin and hypergastrinemia. Gastric cells can become hyperplastic and form fundic gland polyps (FGPs) in up to 7% to 10% of patients taking PPIs for ≥12 months. Such polyps are benign and typically regress with the discontinuation of PPI. An exception to the benign nature of FGPs is patients with a history of familial adenomatous polyposis, in which FGPs may progress and become dysplastic. A study reported a significantly lower rate of FGP dysplasia in patients taking PPIs,[28] which led to the recommendation that patients with familial adenomatous polyposis and FGPs receive PPIs for chemoprevention.

Long-term PPI use can result in enterochromaffin-like cell hyperplasia and hypergastrinemia, as mentioned above. Hypergastrinemia has raised the concern of long-term PPI use possibly predisposing some patients to the development of neuroendocrine tumors. Of note, gastric carcinoids have been observed in rodents given PPIs. No formal studies have been conducted to evaluate whether such an effect is seen in humans, despite an increased incidence of these rare tumors in population studies of patients using PPIs long term.[29] One analysis has shown that this increase has paralleled the use of PPIs.[30] The fact that gastric carcinoids are extremely rare largely precludes prospective trials to analyze whether such a relationship exists.

Rebound dyspepsia after discontinuation of PPIs has long been a known entity. Several mechanisms of rebound and tolerance have been described, although their relative importance is uncertain.[31] The primary mechanism appears to be sustained hypergastrinemia leading to increased gastric acid–secreting capability that becomes apparent once the drug is discontinued. Such symptoms have been seen in up to 40% of patients who previously had no symptoms. Symptoms can take 2 to 3 months to resolve, depending on dose and duration of therapy.[32] It therefore seems appropriate to consider tapering when discontinuing PPIs in patients who do not appear to be responding or have lost response to treatment.

Gastric acid plays a principal role in sterilizing contents entering the digestive tract. Thus, reduction in gastric acid has been associated with an increased risk of both enteric and systemic infections. Of particular interest is the increased incidence of *Clostridium difficile* colitis. Studies have indicated a pooled odds ratio of 1.96 (95% confidence interval 1.28–3.0) for PPI and antibiotic use, with a greater increase in patients with chronic renal failure and those who are hospitalized. Such an increase is thought to be secondary to higher pH, leading to a more virulent strain and delay in gastric emptying, which prolongs exposure to the organism.[33] Although an increase in *C difficile* has been noted during the past 2 decades, coinciding with use of PPIs, it is possible that this is secondary to more virulent strains that have emerged. It therefore seems appropriate to consider the risks of prescribing PPIs to individuals at risk for *C difficile*, including immunocompromised, elderly, hospitalized patients and those taking cyclic antibiotics. These concerns have led the US Food and Drug Administration (FDA) to issue a safety announcement regarding the use of PPIs and incidence of *C difficile*, stating that a diagnosis of *C difficile* should be considered for people taking PPIs who develop diarrhea that does not improve.

There have also been reports of an association between PPIs and community-acquired pneumonia (CAP). Abnormal gastric colonization and increased microorganisms associated with increased gastric pH leading to aspiration are theoretical risks of PPI use. PPI therapy started within 30 days was associated with an increased risk for CAP, although longer-term use was not.[34] A meta-analysis confirmed this finding and found no association between chronic PPI use and CAP. No convincing data have suggested a strong association.[35]

Chronic PPI use has been associated with fractures and osteoporosis.[36,37] Although randomized controlled trials have not found an increased risk of fractures, seven epidemiologic studies have been done, six of which have shown increased risk with dose of drug and duration of exposure. Support for this evidence comes from a causal relationship noted between acid suppression and reduced absorption of mineral calcium in the diet.[38,39] This has prompted the FDA to recommend that physicians exercise more caution when prescribing PPIs and add safety information about the possible increased risk of hip, wrist, and spine fractures. Three epidemiologic studies, however, have not shown an association with PPI use,[40–42] suggesting that there may be no direct relationship, and those patients who were prescribed PPIs are prone to osteoporosis because of their general health condition.

Another concern is the association between long-term PPI use and hypomagnesemia. In March 2011, the FDA issued an advisory warning that patients taking PPIs may be at risk for hypomagnesemia.[43] There have been 30 cases of severe hypomagnesemia reported in long-term PPI users that normalized after the PPI was discontinued. Although the mechanism is not known, in some patients, PPIs appear to interfere with active transport of magnesium across the intestinal wall or cause excessive loss into the intestinal lumen.[44] It is therefore recommended that before initiating patients into PPIs for long-term therapy (≥1 year) and when coadministered with diuretics or digoxin, serum magnesium levels should be obtained and monitored periodically.

Usage Issues

Although significant overlap exists between EE and nonerosive reflux disease (NERD), it is estimated that 40% to 50% of patients with typical reflux symptoms have non-EE.[45] It is believed that patients with true EE and treated with PPIs may develop healed EE, therefore being misclassified as having NERD.[46] It has therefore been suggested that patients with reflux-like symptoms have upper endoscopy while off PPI for

accurate endoscopic diagnosis. This distinction is important because lower and slower response rates to PPIs have been noted in NERD as compared with EE.[47,48] This is possibly related to underlying *H pylori* infection in patients with NERD, as noted in a 2009 meta-analysis.[49] Therefore, a test-and-treat strategy may be used in which a trial of PPI may be initiated, and if symptoms are refractory to treatment, then testing and treating *H pylori* may be undertaken.

A related topic that is often as controversial is that of PPI use in nonulcer dyspepsia. The rationale for the use of antisecretory agents is based on the hypothesis that either acid sensitivity is abnormal or acid secretion is disturbed in the gastroduodenal region.[50] The acid-secretory agent of choice is a PPI because they have been shown to have more prolonged acid suppression of H2 receptor antagonists. Symptom relief has been shown to be on the order of approximately 70%. A systematic review concluded that PPI therapy may be a cost-effective strategy in the management of nonulcer dyspepsia, provided generic prices are used.[51] There also has been evidence to suggest that many patients benefit from promotility drugs rather than acid suppression.[52] Thus, PPIs do appear to have good clinical benefit in patients with nonulcer dyspepsia; however, in those who fail to respond to therapy, PPIs should be discontinued.

In patients who fail PPI once-daily treatment for both healing EE and symptom relief of GERD, two strategies are often used. Switching to another PPI is one strategy and doubling PPI dose is the more common strategy. Although the latter is the strategy recommended by the 2008 American Gastroenterological Association guidelines for GERD, there is no PPI dose-response relationship for EE or NERD.[53] If double-dose therapy is to be considered, PPI should be taken before eating breakfast and before eating dinner on the basis of studies showing improved control of gastric pH when PPI is taken twice per day as opposed to taking two pills before breakfast.[54] Patients should be advised regarding the increased risk of adverse effects before initiating twice-daily therapy.

The economic impact of overprescribing PPIs should not be disregarded. Between 25% and 70% of patients who take these drugs long term do not have an appropriate indication.[55] A retrospective review of 946 patients conducted in an ambulatory care setting found only 35% of the patients were given PPIs for an appropriately documented upper gastrointestinal tract diagnosis, whereas the remaining patients were given PPIs for either extraesophageal symptoms, unclear gastroprotection, or no documented appropriate indication.[56] The total yearly cost excess was estimated at $233,994 based on over-the-counter PPIs, and $1,566,252 based on average wholesale price costs.[57] Coupled with the fact that on-demand therapy for moderate to severe NERD has been shown to be a cost-effective approach,[57] overprescribing PPIs has a significant impact on healthcare expenditures.

With the widespread use of PPIs, the delay in diagnosis of Zollinger-Ellison syndrome becomes an issue. Symptoms of Zollinger-Ellison syndrome are almost exclusively secondary to effects of gastric acid hypersecretion.[58] PPI use controls the acid hypersecretion in virtually all patients with gastrinoma,[59] suggesting that only those patients with refractory symptoms will be diagnosed correctly. Support for this notion was provided in a study indicating that since PPIs have been released, fewer new patients with gastrinoma have been diagnosed and fewer patients have been referred for workup, leading to the conclusion that diagnosis of gastrinoma is often delayed and patients are subsequently diagnosed at more advanced stages in their disease course.[59] Additional support for this hypothesis comes from a study in which surgeons reported seeing patients with more advanced gastrinoma disease when 5-year cure rates are less likely.[60] Physicians are therefore obligated to maintain an index of suspicion for this disease in a patient with prolonged symptoms being treated with PPIs.

Conclusions

Absolute indications for PPI use include PUD, chronic NSAID use, treatment of *H pylori* infection, and EE. Further studies are needed to establish treatment duration after *H pylori* clearance for bleeding PUD and for chemoprophylaxis in Barrett esophagus. PPIs are not without significant adverse effects; therefore, their long-term use must be reevaluated periodically and discontinued when appropriate. This specifically applies to patients with NERD or PUD and patients taking double-dose PPI, from which questionable benefit is obtained. After 20 years of experience with these drugs, many caveats apply to their use.

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