Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders

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INTRODUCTION

Proton pump inhibitors (PPIs) effectively block gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane.

This topic review will provide an overview of the mechanism of action, pharmacokinetics, administration, and adverse effects of PPIs. The use and efficacy of PPIs in specific acid-related disorders is presented separately. (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects".)

INDICATIONS FOR PPI THERAPY

Proton pump inhibitor (PPI) therapy is indicated in the following clinical situations:

- **Peptic ulcer disease** – PPIs are first-line antisecretory therapy in the treatment of peptic ulcer disease. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Initial antisecretory therapy'.)

- **Gastroesophageal reflux disease** – PPIs are indicated in patients with gastroesophageal reflux disease, including for the treatment of erosive esophagitis and as maintenance therapy in patients with severe erosive esophagitis or Barrett's esophagus. (See "Medical

management of gastroesophageal reflux disease in adults", section on 'Severe or frequent symptoms or erosive esophagitis'.)

- **Zollinger-Ellison syndrome** – PPIs, often in high doses, are required to control gastric acid hypersecretion in patients with gastrin-secreting tumors. (See "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)", section on 'Proton pump inhibitors'.)

- **NSAID-associated ulcers** – PPIs are indicated in the primary prevention of gastroduodenal ulcers associated with NSAID use. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

- **Eradication of *Helicobacter pylori*** – PPIs are a component of several first-line and salvage therapy regimens for *H. pylori* infection. (See "Treatment regimens for Helicobacter pylori in adults".)

PHARMACOLOGY

- **Mechanism of action** – Proton pump inhibitors (PPIs) inhibit H-K-ATPase, the final step of gastric acid secretion by parietal cells.

  PPIs are benzimidazole prodrugs which accumulate specifically and selectively in the secretory canaliculus of the parietal cell [1]. Within that space, they undergo an acid catalyzed conversion to a reactive species, the thiophilic sulfonamides, which are permanent cations. The rate of conversion varies among the compounds and is inversely proportional to the pKa of the benzimidazole (rabeprazole >omeprazole, esomeprazole, and lansoprazole >pantoprazole) (table 1) [2]. The reactive species interacts with the external surface of the H-K-ATPase that faces the lumen of the secretory space of the parietal cell, resulting in disulfide bond formation with cysteine 813 located within the alpha-subunit of the enzyme; this is the residue that is intimately involved in hydrogen ion transport. This covalent inhibition of the enzyme results in a specific and long-lasting impairment of gastric acid secretion. (See "Physiology of gastric acid secretion".)

- **Pharmacokinetics** – PPIs are similar in structure and mechanism of action, but PPIs differ in their pKa, bioavailability, peak plasma levels, and route of excretion (table 1). The magnitude of these differences are small and their clinical relevance has not been established.

PPIs are most effective when the parietal cell is stimulated to secrete acid postprandially, a relationship that has important clinical implications for timing of administration. Because the amount of H-K-ATPase present in the parietal cell is greatest after a prolonged fast, PPIs should be administered before the first meal of the day. In most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition, and a second dose, which is occasionally necessary, should be administered before the evening meal [1]. (See 'Dose and timing of administration' below.)

Once-daily PPI dosing for five days inhibits maximal gastric acid output by approximately 66 percent. Since PPIs inhibit only activated enzyme present in the canalicular membrane, the reduction of gastric acid secretion after an initial dose will probably be suboptimal. As inactive enzyme is recruited into the secretory canaliculus, acid secretion will resume, albeit at a reduced level. After the second dose is given on the next day, more H-K-ATPase will have been recruited and subsequently inhibited, and after the third dose, additional recruitment and further acid inhibition will probably occur. Thus, the occasional use of a PPI taken on an "as needed" basis does not reliably provide adequate acid inhibition and does not produce a consistent or satisfactory clinical response (in contrast to the H2 antagonists, which have a more rapid onset of action) [1].

Restoration of acid secretion after discontinuing PPIs depends upon enzyme turnover and the biological reversibility of the disulfide bond. Maximal acid secretory capacity may not be restored for 24 to 48 hours [1]. (See 'Discontinuing PPIs' below.)

- **Metabolism** – PPIs are metabolized via hepatic cytochrome P450 enzymes, with CYP2C19 having the dominant role. However, the dominance of CYP2C19 over other pathways varies significantly among the PPIs (table 2). The activity of CYP2C19 is also determined to some extent by genetic polymorphisms. Two inactivating mutations have been described as a result; the metabolism of PPIs by this route may be delayed in these individuals [3,4]. Homozygotes for the wild type gene rapidly metabolize these drugs, while heterozygotes are intermediate metabolizers.

  Plasma levels of PPI correlate with their metabolism, and differences may contribute to varying dose requirements and clinical efficacy. As an example, one study examined the effect of variable metabolism of omeprazole when using this agent to treat *H. pylori* in 62 Japanese patients [3]. While eradication was achieved in all individuals homozygous for a *CYP2C19* mutation (ie, slow metabolizers), successful treatment was achieved in only 60 and 29 percent of heterozygotes and wild type homozygotes, respectively. In another study that evaluated the efficacy of lansoprazole in the treatment of 65 patients with gastroesophageal reflux disease (GERD), slow metabolizers were much more likely to be

asymptomatic as compared with heterozygotes and wild type homozygotes (85 versus 68 and 46 percent, respectively) [5]. The response rate in wild type homozygotes with severe GERD was only 16 percent. Wild type homozygotes (rapid metabolizers) also had the lowest plasma lansoprazole concentrations. (See 'Dose and timing of administration' below.)

PRETREATMENT CONSIDERATIONS AND MONITORING

Drug interactions — Clinically important drug interactions with proton pump inhibitors (PPIs) are rare. However, PPI metabolism via hepatic cytochrome P450 enzymes may lead to specific drug interactions in some individuals. The presence of a *CYP2C19* gene mutation results in higher plasma PPI levels in homozygous individuals. However, if this metabolic pathway becomes saturated, the isoenzyme can become a major target for interactions with many drugs, including warfarin, diazepam, clopidogrel, and phenytoin (table 3). CYP3A4-mediated metabolism may also be activated under such conditions and become the principal route of drug elimination. Furthermore, induction of CYP1A, another P450 isoenzyme, in CYP2C19 deficient or saturated individuals, can make them susceptible to interference with theophylline metabolism. The specific P450 enzymes involved in PPI metabolism and the potential for interactions among PPIs varies considerably (table 2) [6-12].

Some other important drug interactions with PPIs include the following:

- Clopidogrel **-** Some data suggest decreased activation of clopidogrel when used in conjunction with omeprazole due to shared hepatic cytochrome P450-mediated metabolism. In 2009, the United States Food and Drug Administration concluded that patients taking clopidogrel should consult with their clinician if they are taking or considering taking a PPI, including over-the-counter PPI preparations [13,14]. However, the relevance of these data remains highly controversial. The interaction of clopidogrel and PPIs are discussed in detail separately. (See "Clopidogrel resistance and clopidogrel treatment failure".)

- **HIV protease inhibitors -** PPIs may decrease the absorption of certain HIV protease inhibitors. PPIs are contraindicated in patients being treated with rilpivirine. Atazanavir should not be used in patients who require a PPI dose equivalent to >20 mg omeprazole daily. (See "Overview of antiretroviral agents used to treat HIV", section on 'Protease inhibitors (PIs)'.)

- Methotrexate - Coadministration of PPIs with high dose methotrexate appears to be correlated with delayed methotrexate elimination and potentially may lead to methotrexate toxicity if not monitored appropriately.

For additional information on drug interactions, use the Lexicomp drug interactions program provided by UpToDate. (See "Overview of the nonacute management of unstable angina and non-ST-elevation myocardial infarction", section on 'Gastrointestinal prophylaxis'.)

Laboratory testing — We limit routine laboratory testing to selected patients on PPI therapy.

- **Magnesium** – We obtain serum magnesium levels prior to starting a PPI in patients who are expected to be on long-term (≥1 year) treatment or in patients who take PPIs in conjunction with other medications associated with hypomagnesemia (eg, diuretics). In addition, we obtain magnesium levels periodically in such patients while they are taking a PPI. The frequency of testing is based on the clinical history and the presence of symptoms of hypomagnesemia. As an example, in patients with a history of arrhythmias or QT interval prolongation, we monitor magnesium levels every six months. The management of hypomagnesemia is discussed in detail separately. (See "Hypomagnesemia: Evaluation and treatment".)

- **Vitamin B12** – We also obtain vitamin B12 levels yearly in patients on long-term PPIs [15]. However, routinely monitoring vitamin B12 levels is controversial. (See 'Magnesium malabsorption' below and 'Vitamin B12 malabsorption' below.)

There are insufficient evidence to support routine bone density monitoring or calcium supplementation due to proton pump inhibitor use alone [16].

ADMINISTRATION

Intravenous regimen — IV PPIs are indicated prior to endoscopic evaluation in patients with clinically significant upper gastrointestinal bleeding from a suspected peptic ulcer. Pantoprazole and esomeprazole are the only PPIs available as an IV formulation in the United States; IV omeprazole is available in other countries. The use of PPIs in the treatment of bleeding peptic ulcers and the duration of treatment is discussed in detail separately. (See "Overview of the treatment of bleeding peptic ulcers", section on 'Oral versus intravenous dosing' and "Approach to acute upper gastrointestinal bleeding in adults", section on 'Acid suppression'.)

Oral regimen

Selecting a PPI — The choice of a specific oral PPI and whether over-the-counter (rather than prescription) PPIs are prescribed are often determined by patient preference and payer coverage. A systematic review of 12 randomized trials examining the relative effectiveness of different PPI doses and dosing regimens found no consistent difference in symptom resolution and esophagitis healing rates [17].

In patients unable to swallow pills or capsules, options include an oral suspension of lansoprazole and a powder formulation of omeprazole-sodium bicarbonate for oral suspension.

Dose and timing of administration — PPIs should be administered 30 to 60 minutes before breakfast for maximal inhibition of proton pumps. (See 'Pharmacology' above.)

Dose reduction, particularly for maintenance of healing of erosive esophagitis may be possible in Asian populations. Polymorphisms in the *CYP2C19* gene, which encodes the cytochrome P450 isoenzyme that metabolizes different PPI preparations, are common in Asian and other populations [18]. Such gene mutations would render an individual a "slow metabolizer" and prolong the antisecretory effect of PPIs. In contrast, the duration of acid inhibition would be decreased in a "rapid metabolizer," and differences in PPI metabolism might account for incomplete inhibition of acid secretion and a high prevalence of nocturnal breakthrough symptoms in gastroesophageal reflux disease patients. (See 'Pharmacology' above and "Approach to refractory gastroesophageal reflux disease in adults", section on 'Differences in PPI metabolism'.)

Avoidance of concurrent antisecretory agents — PPIs should not administered concomitantly with antisecretory agents including histamine-2 receptor antagonists (H2RAs), analogues of prostaglandin E (eg, misoprostol), and somatostatin analogues (eg, octreotide), because of the marked reduction in acid inhibitory effects [1,19]. Antisecretory drugs can be used with a PPI provided that there is a sufficient time interval between their administration. As an example, an H2RA can be taken before bedtime or during the night by individuals who report nocturnal breakthrough symptoms such as heartburn after taking a PPI in the morning or before dinner.

Switching between PPIs — Switching PPIs is a reasonable strategy in patients with side-effects to an individual PPI and may be necessary due to cost differences. Although there is significant interindividual and intraindividual variability in intragastric pH control between PPIs, there are no consistent difference in relation to symptom resolution and esophagitis healing rates [17]. Switching PPIs in patients with well-controlled symptoms may also be associated with increased symptom severity and decreased patient satisfaction [20]. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Subsequent management'.)

Discontinuing PPIs — PPIs should be prescribed at the lowest dose and for the shortest duration appropriate to the condition being treated. (See 'Indications for PPI therapy' above.)

We gradually taper PPI therapy in patients treated with PPIs for longer than six months. For patients on a standard or high-dose PPI (eg, omeprazole 40 mg daily or twice daily), we decrease the dose by 50 percent every week. For patients on twice daily dosing, the initial reduction can be accomplished by decreasing the dosing to once in the morning before breakfast until the patient is on the lowest dose of the medication. Once on the lowest dose for one week, the patient is instructed to discontinue the PPI. However, no specific method for discontinuing PPI therapy has been proven effective, and no approach is universally accepted. [21,22].

Studies have demonstrated rebound gastric acid hypersecretion following discontinuation of PPIs in patients with long-term use. The reasons are not entirely clear, but appear to be due in part to the suppression of antral somatostatin expression, resulting in an increase in antral gastrin release and subsequent disruption of normal pH-related feedback inhibition of acid secretion that occurs after a meal [1]. (See "Physiology of gastric acid secretion", section on 'Tolerance'.)

ADVERSE EFFECTS

Long-term PPI use has been associated with several safety concerns. However, few of these concerns are supported by consistent data demonstrating a causal relationship. (See "Physiology of gastrin", section on 'Hypergastrinemia'.)

Gastrointestinal effects

Clostridioides difficile and other enteric infections — PPI use has been associated with an increased risk of *C. difficile* infection, even in the absence of antibiotic use [23-33]. Associations with other enteric infections, including salmonellosis and campylobacteriosis, have also been reported [34-39]. However, the pathophysiologic mechanism involved in the increased risk of infection is unclear.

A 2017 meta-analysis of 50 observational studies found that PPI use was significantly associated with an increased risk of *C. difficile* infection (relative risk [RR] 1.3; 95% CI 1.1-14). The risk of *C. difficile* infection appears to be greater with PPIs as compared to H2 receptor antagonists [30,31].

PPI use has also been associated with an increased risk of recurrent *C. difficile* infection [31]. In a 2017 meta-analysis of 16 observational studies that included 7703 patients with *C. difficile* infection of whom 1525 (20 percent) had recurrent *C. difficile* infection, gastric acid suppression was significantly associated with an increased risk of recurrent *C. difficile* infection (odds ratio [OR] 1.5; 95% CI 1.2-1.9) [40]. There was significant heterogeneity among the studies included in the meta-analysis. In adjusted analysis using data from nine studies, PPI use was associated with an increased risk of recurrent *C. difficile* infection after controlling for patient age and other co-morbid conditions (OR 1.4; 95% CI 1.1-1.8). (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Gastric acid suppression'.)

Microscopic colitis — PPI use has been associated with microscopic colitis, including lymphocytic and collagenous colitis. In a case-control study that included 95 cases of microscopic colitis, exposure to PPIs was significantly higher in patients with microscopic colitis as compared with controls (38 versus 13 percent, OR 4.5, 95% CI 2.0-9.5) [41]. Similar results have been reported in other case-control studies, however, it is unclear if this association varies by PPI and if there is a dose-response relationship in either dose or duration of use [42,43]. (See "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management", section on 'Medications'.)

Hypergastrinemia — Induction of hypergastrinemia has been associated with gastric carcinoid tumors in rats. However, these observations are not generalizable to species with gastrin physiology more analogous to humans [44]. While patients treated with omeprazole for up to 11 years have shown some enterochromaffin-like cell hyperplasia, no dysplasia or neoplastic changes have been observed [45]. An increased risk of colon cancer due to hypergastrinemia has also not been established [46]. (See "Physiology of gastrin".)

Atrophic gastritis — Patients on long-term PPI therapy have a propensity to develop chronic atrophic gastritis. However, the risk of atrophic gastritis is small, and in the rare patient who develops atrophic gastritis, the clinical consequences are uncertain [45,47,48]. (See "Risk factors for gastric cancer".)

Intestinal colonization of multi-drug resistant organisms — PPIs may increase the risk of intestinal colonization with multi-drug resistant organisms. In a meta-analysis of 12 observational studies that included 22,305 patients, after adjusting for potential confounders, acid suppression increased the odds of intestinal carriage of multi-drug resistant organisms of the *Enterobacterales* order (producing extended-spectrum beta-lactamases, carbapenemases, or plasmid-mediated AmpC beta-lactamases) and of vancomycin-resistant enterococci (OR 1.74; 95% CI 1.4-2.2) [49]. Possible mechanisms include an increase in bacteria that survive transit

from the stomach to the intestine due to reduction in gastric acid by PPIs and direct alteration of the composition of intestinal microbiota, leading to a decrease in mean species diversity.

Inflammatory bowel disease — In a study that pooled data from three observational cohorts and included >600,000 individuals followed for a median of 12 years, the risk of inflammatory bowel disease (IBD) was increased in regular PPI users as compared with nonusers (hazard ratio [HR] 1.42; 95% CI 1.22–1.65) [50]. However, the absolute risk of IBD was low, with a number needed to harm of 3770. In addition, absence of data on PPI dosing precluded assessment of a dose-response relationship between PPI use and IBD.

Malabsorption of minerals and vitamins

Magnesium malabsorption — PPIs can cause hypomagnesemia due to reduced intestinal absorption [51]. A meta-analysis of nine observational studies that included a total of 109,798 patients found that those who took a PPI had a significantly higher risk (RR 1.43; 95% CI 1.08-1.88) of developing hypomagnesemia as compared with those who did not [52]. Clinical manifestations of hypomagnesemia include neuromuscular excitability (eg, tremor, tetany, convulsions), weakness, and apathy. Severe PPI-induced hypomagnesemia has been associated with QT interval prolongation and torsades de pointes [53,54]. The risk of hypomagnesemia appears to be mainly in patients who have been on PPIs long-term (generally longer than one year) but cases have been reported within one year of starting PPI therapy [53,55]. This potential risk has led to recommendations to monitor serum magnesium levels in specific patients at high risk for hypomagnesemia. Monitoring for hypomagnesemia in patients on PPIs is discussed in detail separately. (See 'Laboratory testing' above and "Hypomagnesemia: Clinical manifestations of magnesium depletion", section on 'Overview of clinical manifestations'.)

Calcium and fracture risk — Although hypochlorhydria could theoretically reduce calcium absorption, the effect appears to be relevant only for the absorption of water insoluble calcium (eg, calcium carbonate) and can be overcome by ingestion of a slightly acidic meal [56]. The absorption of water soluble calcium salts or calcium in dairy products are not impacted by PPI-induced hypochlorhydria. When calcium supplementation is necessary in patients taking PPIs, we use calcium supplements that do not require acid for absorption, such as calcium citrate. (See 'Laboratory testing' above and "Drugs that affect bone metabolism", section on 'Proton pump inhibitors'.)

PPI-induced hypochlorhydria can augment osteoclastic activity, thereby decreasing bone density [57,58]. Although an association between PPI use and bone fracture is plausible, causality has not been established [59]. Nonetheless, the FDA has mandated revised safety information on all PPIs about a possible increased risk of fractures of the hip, wrist, and spine

with the use of these medications [60]. The association between PPIs and bone metabolism and risk of fracture are discussed in detail separately. (See "Drugs that affect bone metabolism", section on 'Proton pump inhibitors'.)

Vitamin B12 malabsorption — Long-term therapy with PPIs has been associated with vitamin B12 malabsorption [61,62]. However, absorption of oral B12 supplements is not affected. (See 'Laboratory testing' above and "Treatment of vitamin B12 and folate deficiencies", section on 'Treatment of vitamin B12 deficiency'.)

Iron malabsorption — Gastric acid plays a role in the absorption of nonheme iron, and the use of PPIs has been associated with decreased iron absorption [63-67]. However, in most cases the decreased absorption does not appear to be of clinical significance. One exception may be in patients who require oral iron supplementation [66,68]. Such patients may need a higher dose or longer duration of supplementation [66]. (See "Treatment of iron deficiency anemia in adults", section on 'Dosing and administration (oral iron)'.)

Kidney disease — PPIs can cause acute interstitial nephritis (AIN) [69-72]. Similar to other cases of drug-induced AIN, AIN due to PPI use is not dose-dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug. (See "Clinical manifestations and diagnosis of acute interstitial nephritis", section on 'Drugs'.)

PPI use has also been associated with an increased risk of incident chronic kidney disease (CKD), CKD progression, and end-stage kidney disease [73-76]. However, the mechanism underlying the association between PPI use and risk of CKD is not known, and it is possible that the weak association observed in these studies is due to methodological limitations (residual confounding) [73,74,77]. Further studies are needed to help better define an etiologic relationship between PPI use and the development and worsening of CKD.

Drug-induced lupus — In postmarketing safety surveillance, new onset of cutaneous lupus erythematosus and systemic lupus erythematosus (SLE), and exacerbation of existing disease have been reported in patients on PPIs [78-80]. Most cases of CLE-associated with PPI use are subacute and occur within weeks to years after continuous PPI therapy. PPI-associated SLE usually occurs days to years after initiating PPI treatment and typically presents with a rash. Most patients improve within 4 to 12 weeks of discontinuation of PPI therapy. (See "Drug-induced lupus", section on 'Causative drugs'.)

Other associations of unclear significance

COVID-19 — It is unclear if PPI use is associated with an increased risk of COVID-19. In a cross-sectional survey of 86,602 individuals, 53,130 reported prior abdominal pain, acid reflux,

heartburn, and regurgitation symptoms and provided data on H2RA and PPI use. Of these, 3386 individuals (6.4 percent) self-reported a positive COVID-19 test [81]. In analyses adjusted for socioeconomic, lifestyle, and clinical comorbidities, patients who reported PPI use were significantly more likely to report a positive COVID-19 test with a dose-dependent increase in odds of reporting a positive test (PPI once-daily OR 2.15, 95% CI 1.9-2.4; PPI twice-daily OR 3.7, 95% CI 2.9-4.6). It is possible that this association is due to residual confounding.

Other studies have demonstrated that patients taking PPIs are at increased risk for severe clinical outcomes of COVID-19 but have not demonstrated an increase in susceptibility to SARS-CoV-2 infection [82]. These data require further validation.

Dementia — Although some studies have found a significant association between use of PPIs and incident dementia, others have not found an association between PPI use and cognitive function [83-88]. The association between PPI use and dementia may reflect residual confounding by factors related to both use of PPIs and the development of dementia and is discussed in detail, separately. (See "Epidemiology, pathology, and pathogenesis of Alzheimer disease", section on 'Medications'.)

Pneumonia — While observational studies suggest an association between PPI use and pneumonia, the observed association may be due to confounding such that individuals prescribed PPIs may be more likely to have other unobserved health characteristics that predispose them to pneumonia as compared with nonusers [89-96]. (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults", section on 'Predisposing host conditions' and "Risk factors and prevention of hospital-acquired and ventilator-associated pneumonia in adults", section on 'Role of gastric pH'.)

Mortality — It is unclear if PPI use is associated with an increase in risk of death. In an observational cohort study that included 275,977 new PPI users and 73,335 new histamine-2 receptor antagonist (H2RA) users, over a median follow-up of 5.7 years, the incident death rate among new PPI users was higher as compared to those receiving H2RA (4.5 versus 3.3 per 100 person-years) [97]. New PPI users were significantly older as compared with new users of H2RAs at the time of study entry (61.7 versus 58.5 years). However, after adjusting for potential confounders, PPI use was associated with an increase in all-cause mortality as compared with H2RA use (HR 1.25, 95% CI 1.23-1.28). PPI users also had an increase in risk of death as compared with individuals without any PPI use and individuals without any acid suppression use (HR 1.15, 95% CI 1.14-1.15; HR 1.23, 95% CI 1.22-1.24, respectively). Among new PPI users, the risk of death increased with the duration of PPI use. Limitations of the study include its generalizability as the study cohort primarily consisted of older White males, and lack of data on the cause of mortality. The underlying basis for this apparent increased risk of death with PPI

use are not known and further studies are needed to evaluate whether this epidemiologic association is due to unmeasured confounding.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acid reflux and GERD in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Gastroesophageal reflux disease in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Indications for proton pump inhibitors** – Indications include the treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. Proton pump inhibitors (PPIs) are effective in the prevention of nonsteroidal anti-inflammatory drug-associated gastroduodenal mucosal injury and are an important component of several antimicrobial regimens used in the treatment of *Helicobacter pylori* infection. (See 'Indications for PPI therapy' above.)
- **Pharmacology** – PPIs effectively block gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane. Genetically determined variability in the PPI metabolism can influence their efficacy. The presence of a *CYP2C19* gene mutation can result in higher plasma PPI levels in homozygous individuals. PPI metabolism via hepatic cytochrome P450

enzymes may lead to specific drug interactions in some individuals. However, clinically important drug interactions with PPIs are rare. (See 'Pharmacology' above.)

- **Administration** – Oral PPIs should be administered 30 to 60 minutes before breakfast for maximal inhibition of proton pumps. PPIs should not be administered concomitantly with H2-receptor antagonists, and prostaglandins or somatostatin analogues. The magnitude of pharmacokinetic differences between PPIs is small and the clinical relevance of these differences has not been established (table 1). Intravenous PPI therapy is indicated in patients with clinically significant upper gastrointestinal bleeding prior to endoscopy for treatment of suspected bleeding peptic ulcers. In general, PPIs should be prescribed at the lowest dose and for the shortest duration appropriate to the condition being treated. When discontinuing PPI therapy, we taper the dose gradually in patients on PPIs for longer than six months. (See 'Administration' above.)

- **Adverse effects**

  - **Gastrointestinal** – PPI use has been associated with an increased risk of *Clostridioides difficile* infection, other enteric infections, and microscopic colitis. *C. difficile* infection with diarrhea may occur even in the absence of antibiotic use. (See 'Gastrointestinal effects' above.)

  - **Malabsorption of minerals and vitamins**

    - PPIs can cause hypomagnesemia due to reduced intestinal absorption. Long-term therapy with PPIs has been associated with vitamin B12 malabsorption. We obtain serum magnesium levels prior to starting a PPI in patients who are expected to be on long-term (≥1 year) treatment, or in patients who take PPIs in conjunction with other medications associated with hypomagnesemia. In addition, we also monitor magnesium and vitamin B12 levels in patients on long-term PPIs. (See 'Pretreatment considerations and monitoring' above and 'Magnesium malabsorption' above and 'Vitamin B12 malabsorption' above.)

    - Although an association between PPIs and bone fracture is plausible, causality has not been established. PPIs can decrease the absorption of water insoluble calcium (eg, calcium carbonate). When calcium supplementation is necessary in patients taking PPIs, we use calcium supplements that do not require acid for absorption, such as calcium citrate. (See 'Calcium and fracture risk' above.)

  - **Kidney disease** – PPIs can cause acute interstitial nephritis. PPI use has also been associated with an increased risk of incident chronic kidney disease (CKD), CKD

progression, and end-stage renal disease. However, further studies are needed to help better define an etiologic relationship between PPI use and the development and worsening of CKD. (See 'Kidney disease' above.)

- **Associations of unclear significance** – There are conflicting data on the association between PPI use and risk of dementia and pneumonia. It is also unclear if PPI use is associated with an increased risk of death. It is possible that these associations are due to residual confounding and more studies are needed. (See 'Kidney disease' above and 'Dementia' above and 'Mortality' above.)

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Topic 5 Version 52.0

GRAPHICS

Pharmacokinetic properties of proton pump inhibitors in adults

Agent	Regimen tested	Oral bioavailability	Time to peak (hours)	Cmax (micrograms/mL)	AUC_{0-24} (mg•h/L)
Dexlansoprazole	30 mg once daily	Absorbed to a similar extent under fasting and fed conditions	1-2 (peak 1) 4-5 (peak 2)	0.7	3.3
Esomeprazole	20 mg once daily	64% (single dose); 90% (after multiple doses if taken on an empty stomach; bioavailability is reduced by ~50% if taken with food)	1-1.6	2.1 (micromol/L)	4.2 (micromol•h/L)
Lansoprazole	30 mg once daily	85% (taken on an empty stomach; absorption is reduced by ~50% if taken with food)	1.5-3	0.5-1.0	3.2
Omeprazole	20 mg once daily (delayed release capsule)	45% (single dose) Varies by formulation; absorption is significantly increased after multiple doses	0.5-3.5	0.7	3.3

Pantoprazole	40 mg once daily	77%	2-2.5	2.5	5.0
Rabeprazole	20 mg once daily	52%	2-5	0.4-0.48	0.9

AUC_{0-24}: cumulative systemic drug exposure as measured by the area under the plasma concentration versus time curve over 24 hours; Cmax: maximum plasma concentration; pKa: acid dissociation constant transformed by negative log; PPI: proton pump inhibitor.

* Duration of antisecretory effect of PPIs exceeds that predicted by drug half-life due to irreversible binding at site of action (ie, parietal proton pumps).

¶ PPIs are converted to their active form (ie, protonated) when pH of parietal cell is lower than pKa of the individual PPI (ie, in presence of gastric acidity). For detail, refer to accompanying text.

Δ Drug metabolism via hepatic CYP2C19 enzymes is polymorphic; thus, PPI systemic exposure (AUC_{0-24}) can be increased several (ie, 2 to 12) times in patients who are intermediate or poor-metabolizers compared with those who are extensive-metabolizers (ie, most patients). 15-20% of persons of Asian descent are CYP2C19 poor-metabolizer phenotypes.

Prepared with data from: United States prescribing information available at US National Library of Medicine DailyMed website (https://dailymed.nlm.nih.gov/dailymed/index.cfm).

Graphic 72598 Version 6.0

Principal cytochrome P450 enzymes involved in hepatic metabolism

PPI	Primary pathway	Secondary pathway	Sulfotransferase
Omeprazole	CYP2C19	CYP3A4	No
Lansoprazole	CYP3A4	CYP2C19	No
Rabeprazole	CYP2C19	CYP3A4	No
Pantoprazole	CYP2C19	CYP3A4	Yes
Esomeprazole	CYP2C19	CYP3A4	No

PPI: proton pump inhibitor.

Adapted from: Gugler R, Jensen JC, Gastroenterology 1985; 89:1235; Diaz D, Fabre I, Daujat M, et al, Gastroenterology 1990; 99:737; Meyer UA, Eur J Gastroenterol Hepatol 1996; 8 Suppl 1:S21; Parsons ME, Eur J Gastroenterol Hepatol 1996; 8 Suppl 1:S15; Lew EA, Aliment Pharmacol Ther 1999; 13 Suppl 5:11.

Graphic 72565 Version 2.0

Comparison of drug interactions with proton pump inhibitors

Concomitant drug	Omeprazole	Lansoprazole	Rabeprazole	Pantoprazole	Esomepraz
Warfarin	PT decreased by 10 percent	-	-	-	-
Diazepam	T1/2 increased by 130 percent	-	-	-	Decreased clearance
Phenytoin	T1/2 increased by 27 percent	-	-	-	-
Theophylline	-	AUC increased by 10 percent	-	-	Unknown
Digoxin	AUC increased by 10 percent	-	AUC, Cmax, T1/2 increased	-	Unknown
Carbamazepine	AUC increased by 75 percent	-	-	-	Unknown

PT: prothrombin time; Cmax: maximum plasma concentration; AUC: area under the curve.

Adapted from: Gugler R, Jensen JC, Gastroenterology 1985; 89:1235; Diaz D, Fabre I, Daujat M, et al, Gastroenterology 1990; 99:737; Meyer UA, Eur J Gastroenterol Hepatol 1996; 8(Suppl 1):S21; Parsons ME, Eur J Gastroenterol Hepatol 1996; 8(Suppl 1):S15; Lew EA, Aliment Pharmacol Ther 1999; 13(Suppl 5):11; Lorf T, et al, Eur J Clin Pharmacol 2000; 55:733.

Graphic 53616 Version 3.0

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