Original Article

Review On Gastro-Intestinal Drugs: "Proton Pump Inhibitor"

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Abstract

Since their clinical introduction more than 25 years ago, proton pump inhibitors (PPIs) have proven to be invaluable, safe, and effective treatments for a wide range of acid-related disorders. PPIs differ slightly in terms of their pharmacokinetic properties, metabolism, and FDA-approved clinical indications, despite the fact that all members of this class act in a similar manner by inhibiting active parietal cell acid secretion. Nonetheless, they all work well for managing peptic ulcer disease, whether it's simple or complicated, as well as gastroesophageal reflux disease. PPIs can cause breakthrough symptoms in some people, particularly at night, due to their short plasma half-lives and requirement for meal-associated dosing, despite their overall efficacy. To specifically address these limitations, longer-acting PPIs and technology to prolong conventional PPI activity have been developed, which may improve clinical outcomes.

Keyword: Proton pump inhibitors, Review, Pharmacokinetics, Indications, Risk

INTRODUCTION

Proton pump inhibitors (PPIs) have steadily taken the lead in the treatment of acid-related disorders ever since the introduction of omeprazole in 1989.PPIs have demonstrated consistent patient tolerance, excellent safety, and generally superior acid suppression capability when compared to earlier agents such as histamine$_2$-receptor antagonists (H_2RAs), synthetic prostaglandin analogs, and anticholinergics. [1, 2]

The United States Food and Drug Administration (FDA) has approved six PPIs as of 2015 (Table 1). [3] Primary care providers have adopted PPI use frequently, and their inclusion in the arsenal of the modern gastroenterologist is commonplace. PPIs are used to treat esophagitis, nonerosive reflux disease (NERD), peptic ulcer disease (PUD), Zollinger-Ellison syndrome (ZES), and functional dyspepsia, as well as to prevent ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs). [4–6] PPIs are also used to eradicate Helicobacter pylori in conjunction with antibiotics. [7] This review will examine the pharmacokinetics and pharmacodynamics of these drugs and provide an update on both the clinical use of PPIs and the remaining challenges with them, despite the fact that their safety profile was excellent during their first two decades of use. [8,9]

Table 1

Commercially Available Proton Pump Inhibitors in the United States

Drug	Dosages, mg	IV	Liquid or suspension	Generic	Over-the-counter
Omeprazole	10, 20, 40	Yes	No	Yes	Yes
Esomeprazole	20, 40	Yes	Yes	Yes	Yes
Lansoprazole	15, 30	Yes	Yes	Yes	Yes
Dexlansoprazole	30, 60	No	No	No	No
Pantoprazole	20, 40	Yes	Yes	Yes	No
Rabeprazole	20	No	No	Yes	No

WHAT ARE PPIs AND HOW DO THEY WORK?

All PPIs that are currently approved are derivatives of benzimidazole: organic molecules that are heterocyclic and have a pyridine and benzimidazole component that are linked by a methyl sulfinyl group. Omeprazole, the first PPI that was useful in the clinic, was the model for this structure. Even though each drug has distinct substitutions on its pyridine and/or benzimidazole rings, the stereo-isomeric compounds esomeprazole and dexlansoprazole [(10)] are remarkably similar in their pharmacological properties. Subsequently introduced drugs include lansoprazole, pantoprazole, rabeprazole, and the stereo-isomeric compounds esomeprazole and Dexlansoprazole.

Tenatoprazole, a brand-new imidazopyridine PPI, has recently undergone preliminary preclinical and clinical testing. PPIs are membrane-permeable, acid-labile weak bases, and this new subset of PPI with a longer half-life may ultimately offer advantages over its benzimidazole cousins, despite not yet being approved for clinical use. [(10)]These drugs are packaged in a variety of delivery systems to avoid luminal gastric acid's premature activation and degradation. These include gelatine capsules, enteric-coated tablets, and powdered coated granules for suspension. Additionally, they can be packaged with bicarbonate to provide temporary luminal pH neutralization. PPIs are absorbed in the proximal small bowel once they leave the stomach. Imidazopyridines like tenatoprazole, which have a serum half-life of 7 hours, may also overcome this weakness and potentially demonstrate additional clinical benefit in the future. [(10)] There are also intravenous (IV) formulations available for lansoprazole, pantoprazole, and esomeprazole. These formulations provide immediate acid suppression and are well suited for hospitalized patients in whom the oral route of administration is not appropriate. [(10)] The serum half-life of single.

The PPIs are circulated to activated gastric parietal cells, where they concentrate in the acidic secretory canaliculi after being absorbed. With the exception of esomeprazole and Dexlansoprazole, which are nonchiral, a chiral sulfoxide bond is cleaved into active sulfenic acid and/or sulphonamide by the PPI here under acid catalysis. After that, these compounds bind covalently to the cysteine residues on the H+/K+ ATPase, preventing acid secretion until replacement pumps can be synthesized (up to 36 hours). [(10)] Although these compounds are frequently considered to be equally effective in terms of clinical parameters, the specific pharmacologic properties of each PPI vary slightly (Table No. 2).

Table 2

Pharmacokinetic Properties of Proton Pump Inhibitors

	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Bioavailability, %	30–40	64–90	80–85	-	77	52
Time to peak plasma level (tmax, hr)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
Protein binding, %	95	97	97	96	98	96.3
Half-life, hr	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19 CYP3A4	CYP2C19 CYP3A4	CYP2C19

For PPI binding, a meal triggers the active expression of H+/K+ ATPases in the canaliculi. None of the parietal cells or its proton pumps are working during a single meal. A single PPI dose inhibits only about two-thirds of proton pumps, leaving up to one-third uninhibited. As previously inactive enzymes are recruited into the secretory canaliculi during subsequent meals, proton exchange will once more increase—albeit at a reduced rate. Pre-prandial dosing, which is important due to the short serum half-life, and the observation of increasing pharmacologic efficacy of PPIs after multiday treatment are both based on this physiology. [(10)]

Hepatic P450 cytochromes are responsible for the degradation of PPIs, which are highly protein-bound. Omeprazole and its stereo-isomer esomeprazole are metabolized almost entirely by CYP_2C_{19}, offering the greatest potential for interaction with other drugs.[(14)] Despite the fact that the CYP_2C_{19} pathway is the dominant pathway overall, individual agents have variations that have led to concerns regarding efficacy and drug-drug interaction.CYP_2C_{19} also metabolizes rabeprazole and lansoprazole/Dexlansoprazole, but they have a high affinity for CYP_3A_4.With these agents, interactions appear to be less important, possibly because of this difference. Pantoprazole, on the other hand, is mostly degraded by CYP_2C_{19} O-demethylation and sulphate conjugation, so it has the lowest potential for cytochrome induction or inhibition of the benzimidole.[(15)] We usually prescribe pantoprazole or lansoprazole/dexlansoprazole to patients on clopidogrel who are particularly concerned about this interaction of drug metabolism. The majority of benzimidole are eventually excreted through the kidneys after hepatic metabolism, though lansoprazole and dexlansoprazole are also excreted through the biliary tree.[(6)] Although this is a controversial topic, there are data to suggest that patients who are genetically rapid drug

metabolizers—a situation that is more prevalent in Europe and North America—may be less likely to fully respond to their PPI treatment, particularly eradication of H.

CLINICAL ADVANTAGES OF PPIs.

The secretion of gastric acid is a multifactorial and intricate process that is influenced by at least three distinct stimuli on the parietal cell. Gastrin and histamine's paracrine elaboration and the actions of postganglionic muscarinic acetylcholine are examples of these pathways. PPIs, in contrast to anticholinergics and histamine 2-receptor blockers, inhibit the H/K ATPase, the final common pathway of acid secretion, upon any stimulation of the parietal cell. [1, 16]

Because they directly block the acid pump itself, the PPIs are the most potent inhibitors of gastric acid secretion that are currently available. PPIs outperform H_2RAs in terms of postprandial and nocturnal intragastric pH control, which is of clinical importance in some patients, and their superior biochemical effect is maintained over the long term without the need for dose escalation.[16] This superior biochemical effect is based on their ability to reliably maintain intragastric pH >4 for between 15 and 21 hours daily, as opposed to only 8 hours for H_2RAs.[17] H_2RAs, on the other hand, can cause tachyphylaxis as quickly as 3 to 5 days after regular use.[18] While this difference may not matter in the short term, the acid-suppressing effect of H2RAs can be nearly cut in half with regular use. [19]

GENERAL CLINICAL USES OF PPIs.

1. Healing of PUD

Acid suppression remains the mainstay of treatment for both gastric and duodenal ulcer disease, despite their distinct underlying pathophysiology's. In both cases, a significant factor in healing is the sustained neutralization of gastric acid (pH>3) over 18 to 20 hours per day. [2, 20]

PPI therapy has consistently demonstrated superior healing rates for gastroduodenal ulcers compared to H_2RAs in clinical trials. An overall therapeutic gain of 15.2% in healing for duodenal ulcers (p0.001) and 9.9% for gastric ulcers (p0.005) after only two weeks of treatment was found in a meta-analysis that compared omeprazole (20 mg daily) to either ranitidine or cimetidine. When treated with PPIs, a greater proportion of patients also had no symptoms at first follow-up. [21] Pooled data from 384 randomized controlled trials (RCTs) with 44,870 patients found that omeprazole was significantly more effective (p=0.001) than H_2RAs at healing ulcers, with overall rates of 80.8% and 74.7%, respectively. [22] Similar results with lansoprazole, rabeprazole, and pantoprazole. [25]

In high-risk patient groups, such as those with PUD-related complications, recurrences, or H. pylori negative ulcers, maintenance therapy is an important option after initial healing. There are similar data for maintenance and prevention with lansoprazole (15 mg) [27]. Although clinical trials describe dosing of PPIs for maintenance for up to 12 months, the ideal duration of therapy is not known, and prolonged treatment may be unnecessary if H. pylori is eradicated. In a RCT involving 195 patients, the incidence of recurrent duodenal ulcer was reduced from 67% to 23% when compared to placebo (p0.001). We favour the prolonged use of PPIs when coincident clinical concerns exist (e.g., persistent symptoms), when H_2RAs have proven ineffective, in the setting of NSAID-associated or non-H. pylori-related ulcer, or when there have been ulcer-related complications (e.g., perforation and fibrosis) at the outset. It should also be noted that the continuous use of H_2RAs is similarly effective at preventing ulcer recurrence.

2. Peptic ulcer related gastrointestinal bleeding

Although modern societal recommendations emphasize rapid assessment, the best supportive care, and prompt endoscopic diagnosis and haemostasis, the method and dosage of antisecretory PPI therapy remain important considerations [30–32]. Upper gastrointestinal (UGI) bleeding caused by PUD is a significant emergency medical condition that results in extremely high patient morbidity, health care costs, and mortality [.29,30]A Cochrane systematic review of six high-quality RCTs (n=2,223) revealed that overall mortality did not decrease (by 6.1% compared to 5.5%; rebleeding (13.9% versus 16.6%; odds ratio [OR]=1.12, 0.72–1.73)OR=0.81, 0.61–1.09), or surgery (9.9 percent vs. 10.2 percent; Pre-administration of PPI was found to reduce the proportion of patients who had high-risk stigmata of haemorrhage by Forrest classification at the time of initial endoscopic exam (37.2% vs. 46.5%; OR=0.96, 0.68–1.35) in patients who received pre-endoscopic PPI therapy. [33] Despite this lack of improvement in hard outcomes, OR=0.67, 0.54–0.84). Early PPI therapy was also linked to a lower risk of rebleeding (OR=0.38, 0.18–0.81) and a lower need for surgery (OR=0.62, 0.44–0.88) in patients in trials where endoscopic haemostatic therapy was used inconsistently. Our practice is to initiate a high dose IV bolus (pantoprazole or esomeprazole) and continuous infusion until an endoscopic diagnosis can be determined in light of these data and the favourable risk profile of early PPI use. The dosage and continuation of treatment can be tailored to the identified source of bleeding following an endoscopy.

A meta-analysis of intravenous PPI therapy (80 mg bolus followed by 8 mg/hr) versus placebo for 72 hours after endoscopy demonstrated a significant reduction in rebleeding (number needed to treat [NNT] =12), surgery (NNT=28), and mortality (NNT=45) in patients who had high-risk endoscopic stigmata (active bleeding, visible vessel, or adherent clot) at the time of their exam. [34] Other endoscopic stigma.

3. Eradication of H. pylori *infection*

Several high-quality publications, including the Maastricht consensus report and a recent Cochrane systematic review, suggest that the addition of a PPI along with two (triple therapy) or three (quadruple therapy) antibiotics provides a synergistic effect in the eradication of H. pylori and that PPIs are more effective in this role than H_2RAs. [38,39] This benefit has been attributed to both increased bioavailability of acid-labile antibiotic.

Infected patients receiving long-term PPI therapy without H. pylori elimination may face risks, but this is still a contentious issue. In addition, animal data suggest that PPI therapy without eradication may accelerate the potential for H. pylori to induce gastric carcinoma, though there is no substantive human correlation to this model. [44,45] These data highlight the potential importance of eradication confirmation in infected patients who will continue antisecretory therapy beyond the short-course of antibiotics for other clinical purposes. It has been observed that acid-suppression alone alters the pattern of H. pylori-associated gastritis to.

4. Prevention of NSAID induced gastroduodenal ulcers

A multi-society guideline [48] issued in 2008 and an American College of Gastroenterology guideline49 identified patients perceived to be at risk for NSAID induced GI toxicity who should be considered for prophylaxis. NSAID induced GI toxicity is estimated to account for at least 2,600 deaths annually in the United States. [46] In addition, the use or misuse of these drugs causes significant morbidity in the form of UGI symptoms, GI bleeding, and increased health care utilization. [47] Patients who are obligate users of NSAIDs currently have the following options for reducing the risk of GI toxicity associated with NSAIDs: the use of a COX-2-selective nonsteroidal anti-inflammatory drug (NSAID), misoprostol, or acid antisecretory therapy.

Although a few short-term studies of H_2RAs for the prevention of NSAID-induced ulcers have been published [50,51] the findings have not been consistent or observable over the course of long-term patient follow-up. One-day PPIs, on the other hand, were protective against the development of gastroduodenal ulcers (OR=0.35) in asymptomatic patients taking low-dose aspirin who underwent endoscopy. [54] A meta-analysis of 112 individual RCTs by Koch et al. [52] suggested that H_2RAs demonstrated no evidence supporting the use of conventional dose H_2RAs in a prophylactic role, despite the fact that high dose H_2RAs may be beneficial.

Two multicentre studies with higher-risk patients (n=1,429) taking NSAIDs daily provide the strongest evidence in favour of PPI use. In these studies, the group receiving esomeprazole (20 mg daily) had a significantly lower cumulative percentage of patients with ulcers at six months than the group receiving placebo (17%).Additionally, PPI co-therapy significantly reduced ulcer formation in both nonselective and selective NSAID users (6.8% vs. 0.9%), while the use of a selective or nonselective COX inhibitor did not appear to affect whether patients were more likely to develop an ulcer in the placebo group (17.1% vs. 16.5%). [55]

5. Zollinger-Ellison syndrome

PPIs can effectively control the gastric acid hypersecretion associated with ZES, but studies involving a large number of patients are lacking due to the rare nature of the disease. Although the ultimate goal for patients with ZES is surgical excision of the neuroendocrine tumour, virtually every individual with this disease requires medical intervention to prevent acid-peptic complications. [56]

Measured acid output and clinical endpoints were assessed in response to titratable doses of omeprazole in a prospective 4-year study of 40 ZES patients. [57] The majority of patients in the study were able to control their acid output with a once-daily PPI dose, but nine required 60 mg twice daily for acid reduction. Although the usual starting doses for PPIs in ZES are high (typically 60 to 120 mg daily), some patients can be down-titrated as low as 20 mg omeprazole once initial ulcer healing and symptom resolution has occurred. [59] In a separate 13-year series involving 67 patients, more than 90% of those enrolled were able to demonstrate long-term symptom control with a titration of lansoprazole (7.5 to 450 mg/day). [58]

6. Erosive esophagitis

[60, 61] A subset of symptomatic patients will have endoscopic evidence of erosion, though classification of this finding varies among endoscopists. [62] PPIs at typical dosages are exceedingly effective at inducing symptom remission and healing erosive esophagitis the overwhelming majority of patients. [63, 64] A systematic review of 15 epidemiological studies estimates the prevalence of gastroesophageal reflux disease to be somewhere between 10 and 20 percent in the Western world and around 5 percent in Asia.

When compared to H_2RAs and/or prokinetics, a Cochrane review of 134 trials involving 36,978 patients with erosive esophagitis found that the acute use of PPIs consistently resulted in faster esophagitis healing and symptom resolution. This was true regardless of the severity of the initial esophagitis and was also true regardless of treatment duration and dose. Additionally, the overall effectiveness or side effect profile of the currently available PPIs for this indication did not differ significantly. [64]

PPIs are also very good at keeping erosive esophagitis from getting worse. In a landmark 1995 NEJM paper by Vigneri et al. [65], this finding was presented. In this prospective trial, 175 patients with endoscopically confirmed erosive esophagitis were randomly assigned to one of five treatment arms following the initial induction of healing with oral omeprazole (40 mg daily). Among these arms were: omeprazole (20 mg daily), cisapride (10 mg three times daily), ranitidine (150 mg three times daily), or either antisecretory agent in combination with cisapride. Omeprazole alone (or in combination with cisapride) was significantly superior to ranitidine alone (p=0.001), cisapride alone (p=0.003), or both ranitidine and cisapride (p=0.03) in maintaining endoscopic remission after 12 months of maintenance.

Although this study suggested that maintenance doses are typically comparable to those required to elicit initial healing [65], it has since been questioned. With a few exceptions, such as severe esophagitis, half the healing dose of a PPI is typically sufficient for maintenance [66]. As a result, our recommendation is that the lowest dose of PPI required to control

symptoms should be the goal of long-term treatment. Recent guidelines [67] indicate that individuals with milder grades of oesophageal mucosal injury may benefit from switching to on-demand therapy.

7. Nonerosive reflux disease

The gastroenterologist may find NERD, also known as endoscopy-negative reflux disease (ENRD), to be particularly challenging. In patients with no endoscopically evident erosive disease, response rates to PPI and antisecretory treatment have been lower for a variety of possible reasons. The American College of Physicians [69], the American College of Gastroenterology [70], and the American Society for Gastrointestinal Endoscopy [71] continue to support a trial of empiric therapy for undifferentiated gastro-oesophageal reflux disease (GERD) unless alarming clinical indications for immediate upper endoscopy exist. Despite this, PPI treatment for ENRD continues to offer an advantage in terms of heartburn control over H_2RAs (RR=0.78, 0.62–0.97) [68] and On-demand use of PPIs may be a reasonable option for control in patients with intermittent but long-term ENRD symptoms [72, 73] when the absence of significant erosive disease is known.

8. Functional dyspepsia

Around 5% of annual visits to primary care in the United States are for functional dyspepsia, which is either epigastric pain syndrome or postprandial distress syndrome. [74] There is a lot of ongoing debate about the best initial diagnosis and/or treatment for uninvestigated dyspepsia. A Cochrane review further supports the efficacy of PPI treatment in dyspepsia, demonstrating a relative risk reduction in symptoms of 14% (95% confidence interval, 5% to 23%) when compared to placebo. However, treatment with omeprazole (20 mg daily) does have the potential to provide complete symptom relief in patients with dyspeptic symptoms and negative endoscopy when compared with placebo (38 percent vs. 28 percent, p=0.002). [75] Low PPI dosage In this setting, it is difficult to identify individual patients who are likely to respond to antisecretory therapy because GERD, UGI dysmotility, and gastroduodenal acid-peptic disorders frequently share a lot of symptoms. [77]

CLINICAL LIMITATIONS OF PPIs

The widespread availability of PPIs in both over-the-counter and prescription forms, in addition to their consistent therapeutic superiority over H_2RAs, supports the conclusion that these medications cannot be improved. Although a variety of non-PPI-related factors (UGI motility disorders, duodeno-gastric-oesophageal reflux, visceral hypersensitivity, and patient hyper-vigilance) may contribute to this inadequate response, both the short plasma half-life and the requirement for pre-prandial dosing are significant issues. On the other hand, up to 50% of patients taking PPIs for nonerosive GERD are dissatisfied with their treatment due to unresolved. [78]

Among patients taking PPIs two times a day, almost 40% expanded their measurements due to tireless night-time symptoms. [79] Short-term recuperation of gastric corrosive discharge, named "night-time corrosive leap forward," is regularly experienced with once-everyday AM dosing of single delivery PPIs. [80] The heightening of dosing to two times day to day is in many cases acted with regards to both the American Gastroenterology Association [67] and American School of Gastroenterology [81] practice rules. On a twice-daily regimen, many patients continue to experience breakthrough symptoms. [82] Pharmacologically, esomeprazole 40 mg administered twice daily to healthy volunteers still results in an intragastric pH below 4 15% of the time. [83]

Additionally, the significance of drug dosage timing is severely underrated. To establish binding, PPIs require proton pump expression along the parietal cell canaliculi membrane, as previously mentioned. Cytosolic pumps—those located within lipid rafts—will not be affected because they will not be accessible. Poor compliance, combined with a narrow window to provide efficacy due to plasma half-life, may be an important cause of PPI failure [78]. About half of patients do not take their PPIs within one hour of breakfast [79, 82] despite having been instructed to do so by their physician or pharmacist.

1. Long-term use of PPIs

Chronic use of high-dose PPIs is thought to affect the absorption of calcium, magnesium, and vitamin B12 since acid facilitates assimilation and ionization of less soluble forms of dietary calcium and release of food bound vitamin B12. [85] In 2006, a nested, case-controlled series which included more than 13,000 patients from the United Kingdom suggested that the risk of hip fracture was increased with PPI use that exceeded 1 year (OR, 1.44) and was especially increased in those patients who had received high-dose PPIs (OR, 2.65). [86] Although important, this study has received considerable criticism as there was heterogeneity among patients in study arms and a different prevalence of PPI use (e.g., PUD among fracture patients) which could explain the difference in observed fractures without ascribing causality. A later study which did not include patients who had major risk factors for hip fracture showed no association with PPI use and postulated that the earlier findings may have been due to confounding. [87] This pattern of retrospective review and analysis has been consistent within the literature and ultimately the risk posed by PPI use seems unsettled. [88] However, in 2010 the U.S. FDA required all manufacturers of PPIs to revise their product labels to include a warning about possible risk for fractures of the hip, wrist, and spine when used at high dose (more than once daily) or for a long duration (greater than 1 year).

PPI use has also been linked to the development of community-acquired pneumonia, as shown by retrospective observational studies and their meta-analyses. [89, 90] A meta-analysis involving eight observational studies found that PPI use was associated with a 27% increased risk for either hospital-acquired pneumonia or community-acquired pneumonia (OR, 1.27), with the greatest risk occurring within seven days of starting PPI treatment (OR, 3.95). [89] This early risk had

already been shown elsewhere [91] There was no increased risk of pneumonia in a more recent systematic review of trials that only included patients who were prescribed PPI therapy for new-onset NSAID use. In the absence of prospective, high-quality data, this association remains conjectural and does not influence our prescribing of antisecretory therapy to patients with a solid indication, according to the authors of this study. They argue that the previously observed association may have been in part due to protopathic bias, either from the inclusion of GERD patients (a risk factor for pneumonia) or from the misdiagnosis of early symptoms of pneumonia masquerading as GERD. [90]

In addition, there is evidence that PPI use may increase a patient's susceptibility to a variety of enteric infections [92], such as Salmonella, Campylobacter jejune, and Clostridium difficile (CDI). [93] Given the associated morbidity and growing health burden posed by this issue, infection with C. difficile (CDI) is particularly significant. A meta-analysis of 42 observational studies that included over 313,000 patients in 2012 revealed that PPI use was associated with both incident (OR, 1.7) and recurrent (OR, 2.5) CDI. [94] This observation prompted the U.S. Food and Drug Administration (FDA) to issue a drug safety communication emphasizing the significance of PPI exposure. However, the influence of PPI treatment duration and dose on this association is still unknown.

All PPIs are, to some extent, metabolized by the cytochrome P450 isozyme 2C19 as discussed previously. While this pharmacological property of PPIs has been well known for some time, [14] it has more recently become a subject of considerable concern. [15] Specifically, the potential for PPI induced enzyme inhibition to prevent the activation of clopidogrel (Plavix®) has led to a flurry of warnings, revisions, and publications. This interaction was first observed during *in vitro* studies which demonstrated that that synchronous administration of omeprazole diminished the effect of clopidogrel on platelet inhibition. In 2009, the FDA recommended avoiding the use of both drugs simultaneously. [56] Despite this initial concern, there have been no *in vivo* data which has conclusively connected the use of omeprazole and clopidogrel with adverse clinical outcomes. In addition, this *in vivo* association has not been reliably demonstrated with other PPIs that are less dependent on 2C19 for their metabolism. [95] Never the less given our knowledge of the pharmacodynamics, it is our practice to avoid omeprazole (and its stereoisomer, esomeprazole) in patients taking clopidogrel, in favour of alternatives such as lansoprazole, dexlansoprazole, or pantoprazole.

Based on 61 individual case reports, the FDA issued a class warning in 2011 indicating that prolonged PPI use could result in low magnesium levels. PPI-associated acute interstitial nephritis and the possibility of vitamin B12 deficiency with chronic (more than three years) daily PPI use are two other recent FDA mandated PPI class warnings. Although the mechanism responsible for and true incidence of PPI-associated hypomagnesemia are unknown, the FDA recommends checking magnesium levels on a regular basis in patients expected to be on prolonged PPI treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomag.

2. Advances in PPI technology

PPIs' inherent pharmacologic limitations, such as their short plasma half-life (and consequently short duration of effect) and the requirement for pre-prandial dosing, have been the subject of numerous efforts to overcome.

Tenatoprazole, the first imidazopyridine PPI, has demonstrated superior inhibitory activity against H+/K+ ATPase and a significantly longer half-life than currently available PPIs (8 hours after a single dose and 14 hours after multiple doses). Although definitive trials of clinical efficacy are still unavailable, this revision to the structure of PPIs has intriguing potential for the future. [97–99] This increase in half-life correspondingly increases the area under the plasma concentration curve (AUC) by more than 20 times, representing increased tissue exposure and thus duration of effect at the parietal cell canaliculus. As a solution to the difficulties posed by the short serum half-life, modifications to the formulation of currently available PPIs have also been utilized. Rabeprazole-ER comes in a 50 mg capsule with five 10 mg tablets that are meant to be broken down and absorbed in stages throughout the small intestine and colon. Rabeprazole-ER outperformed both esomeprazole and conventional delayed-release rabeprazole in the control of nocturnal gastric acid secretion in healthy subjects in a study [11]; however, in two parallel double-blind studies, rabeprazole-ER was not superior to esomeprazole in the treatment of severe erosive esophagitis (Los Angeles Classification grade C or D) and the alleviation of

The formulation of dual-release dexlansoprazole allows the drug to be released in two distinct pH-controlled phases. At a pH of 5.5, the proximal small intestine releases 25% of the dose, and the pharmacokinetics (peak plasma concentration 1 to 2 hours) are comparable to those of conventional enteric-coated PPIs. A second release of 75% of the dose occurs at a pH of 6.75 in the more distal small intestine, resulting in a second serum peak 5 to 6 hours after administration. This offers a potential advantage to patients with obligate twice-daily dosing for symptom control, [63] persistent nocturnal symptoms, [101] or poor meal timing because, like tenatoprazole, it provides an overall increase in the AUC and, as a result, an overall higher mean 24-hour intragastric pH.12

Include a stimulator of gastric acid secretion alongside the PPI as an alternate strategy to avoid the need for premeal dosing. Succinic acid has been approved by the FDA as a pharmaceutical excipient because it has Penta gastrin-like activity. This substance is "generally recognized as safe" and has previously been utilized in the food and beverage industry as an acidity regulator. A Phase IIb clinical trial (NCT01059383) evaluating heartburn patients is currently in progress. Succinic acid and omeprazole (Vecam®) demonstrated significantly better nocturnal intragastric pH control than omeprazole alone in a preclinical study of 36 healthy subjects. [102]

CONCLUSION

The modern gastroenterologist's arsenal for dealing with everyday clinical issues includes PPIs. In general, they are very effective in treating disorders related to acid. Despite this, the widespread availability and widespread use of PPIs has resulted in increased insurance oversight and legitimate concern regarding the risk of indefinite hypochlorhydria and drug

interactions. Responsible use of any drug, including PPIs, requires the prescriber to carefully consider the appropriate indication, patient cofactors, and anticipated dose and duration of treatment.

Although very effective, PPIs are imperfect drugs owing, at least in part, to their pharmacologic limitations. Several novel approaches to overcome these limitations are being explored including the development of a non-benzimidole PPI and sophisticated delivery systems to mitigate the problems associated with their short half-life and obligatory pre-prandial dosing. Whether these approaches offer a clear clinical advantage or carry with them unanticipated problems, remains to be determined.

REFERENCES

1. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial: Rabeprazole Study Group. Am J Gastroenterol. 2000; 95:1894–1899.
2. Huang JQ, Hunt RH. pH, healing rate and symptom relief in acid-related diseases. Yale J Biol Med. 1996; 69:159–174.
3. U.S. Food and Drug Administration. Proton pump inhibitors: US Food and Drug Administration-approved indications and dosages for use in adults [Internet] Silver Spring: U.S. Food and Drug Administration; 2014. [cited 2016 Aug 31].
4. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997; 112:1798–1810.
5. Lassen AT. Acid-related disorders and use of antisecretory medication. Dan Med Bull. 2007; 54:18–30.
6. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol. 2008; 64:935–951.
7. Klotz U. Pharmacokinetic considerations in the eradication of Helicobacter pylori. Clin Pharmacokinet. 2000; 38:243–270.
8. Esplugues JV, Martí-Cabrera M, Ponce J. Safety of proton pump inhibitors. Med Clin (Barc) 2006; 127:790–795.
9. Maffei M, Desmeules J, Cereda JM, Hadengue A. Side effects of proton pump inhibitors (PPIs) Rev Med Suisse. 2007; 3:1934–1936. 1938.
10. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006; 23(Suppl 2):2–8.
11. Morelli G, Chen H, Rossiter G, Rege B, Lu Y. An open-label, parallel, multiple-dose study comparing the pharmacokinetics and gastric acid suppression of rabeprazole extended-release with esomeprazole 40 mg and rabeprazole delayed-release 20 mg in healthy volunteers. Aliment Pharmacol Ther. 2011; 33:845–854.
12. Vakily M, Zhang W, Wu J, Atkinson SN, Mulford D. Pharmacokinetics and pharmacodynamics of a known active PPI with a novel Dual Delayed Release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials. Curr Med Res Opin. 2009; 25:627–638.
13. Williams MP, Pounder RE. Review article: the pharmacology of rabeprazole. Aliment Pharmacol Ther. 1999; 13(Suppl 3):3–10.
14. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. Ann Intern Med. 1998; 129:1027–1030.
15. Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2011; 12:873–888.
16. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000; 118 (2 Suppl 1):S9–S31.
17. Howden CW. Optimizing the pharmacology of acid control in acid-related disorders. Am J Gastroenterol. 1997; 92(4 Suppl):17S–19S.
18. Wilder-Smith CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS. Tolerance to oral H2-receptor antagonists. Dig Dis Sci. 1990; 35:976–983.
19. Prichard PJ, Jones DB, Yeomans ND, Mihaly GW, Smallwood RA, Louis WJ. The effectiveness of ranitidine in reducing gastric acid-secretion decreases with continued therapy. Br J Clin Pharmacol. 1986; 22:663–668.
20. Hunt RH, Cederberg C, Dent J, et al. Optimizing acid suppression for treatment of acid-related diseases. Dig Dis Sci. 1995; 40(2 Suppl):24S–49S.
21. Eriksson S, Långström G, Rikner L, Carlsson R, Naesdal J. Omeprazole and H2-receptor antagonists in the acute treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis: a meta-analysis. Eur J Gastroenterol Hepatol. 1995; 7:467–475.
22. Morgan DG, Burget DW, Howden CW, et al. Rates of duodenal ulcer (DU) healing by drug classes: a meta-analysis. Gastroenterology. 1993; 104: A150.
23. Poynard T, Lemaire M, Agostini H. Meta-analysis of randomized clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcer. Eur J Gastroenterol Hepatol. 1995; 7:661–665
24. Prakash A, Faulds D. Rabeprazole. Drugs. 1998; 55:261–267.
25. Fitton A, Wiseman L. Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs. 1996; 51:460–482.
26. Lauritsen K, Andersen BN, Laursen LS, et al. Omeprazole 20 mg three days a week and 10 mg daily in prevention of duodenal ulcer relapse: double-blind comparative trial. Gastroenterology. 1991; 100:663–669.
27. Lanza F, Goff J, Silvers D, et al. Prevention of duodenal ulcer recurrence with 15 mg lansoprazole: a double-blind placebo-controlled study. The Lansoprazole Study Group. Dig Dis Sci. 1997; 42:2529–2536.
28. Dammann HG, Walter TA. Efficacy of continuous therapy for peptic ulcer in controlled clinical trials. Aliment Pharmacol Ther. 1993; 7(Suppl 2):17–25. Doi: 10.1111/j.1365-2036. 1993. tb00595. x.
29. Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Lang-man M. Prognostic factors in upper gastrointestinal bleeding. Dig Dis Sci. 1994; 39:706–712. Doi: 10.1007/BF02087411.
30. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012; 107:345–60.
31. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010; 152:101–113
32. Barkun A, Bardou M, Marshall JK Nonvariceal Upper GI Bleeding Consensus Conference Group. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2003; 139:843–857.
33. Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010; (7):CD005415.
34. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. Clin Gastroenterol Hepatol. 2009; 7:33–47. Doi: 10.1016/j.cgh.2008.08.016.
35. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med. 1994; 331:717–727. Doi: 10.1056/NEJM199409153311107.
36. Marshall BJ. Helicobacter pylori. Am J Gastroenterol. 1994; 89(8 Suppl):S116–S128.
37. Shimada T, Yamagata M, Hiraishi H. Role of Helicobacter pylori eradication in the prevention of peptic ulcer in NSAID users. Nihon Rinsho. 2007; 65:1824–1829.
38. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: the Maastricht IV/Florence Consensus report. Gut. 2012; 61:646–664. Doi: 10.1136/gutjnl-2012-302084.
39. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013; (12):CD008337.
40. Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. J Am Pharm Assoc (Wash) 2000; 40:52–62.

41. Lundell L, Havu N, Miettinen P, et al. Changes of gastric mucosal architecture during long-term omeprazole therapy: results of a randomized clinical trial. Aliment Pharmacol Ther. 2006; 23:639–647.
42. Moayyedi P, Wason C, Peacock R, et al. Changing patterns of Helicobacter pylori gastritis in long-standing acid suppression. Helicobacter. 2000; 5:206–214.
43. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, et al. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med. 1996; 334:1018–1022.
44. Hagiwara T, Mukaisho K, Nakayama T, Sugihara H, Hattori T. Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with Helicobacter pylori. Gut. 2011; 60:624–630.
45. Fox JG, Kuipers EJ. Long-term proton pump inhibitor administration, H pylori and gastric cancer: lessons from the gerbil. Gut. 2011; 60:567–568.
46. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med. 1991; 115:787–796.
47. Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. Gastroenterology. 1997; 112:1000–1016.
48. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 Expert Consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents. J Am Coll Cardiol. 2008; 52:1502–1517.
49. Lanza FL, Chan FK, Quigley EM Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009; 104:728–738.
50. Taha AS, Hudson N, Hawkey CJ, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med. 1996; 334:1435–1439.
51. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. Lancet. 2009; 374:119–125.
52. Koch M, Dezi A, Ferrario F, Capurso I. Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta-analysis of randomized controlled clinical trials. Arch Intern Med. 1996; 156:2321–2332.