

An update on the use of pantoprazole as a treatment for gastroesophageal reflux disease

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Abstract: Gastroesophageal reflux disease (GERD) is a chronic, recurrent disease that affects nearly 19 million people in the US. The mainstay of therapy for GERD is acid suppression. Proton pump inhibitors (PPIs) are the most effective medication for both initial treatment and maintenance therapy of GERD. Pantoprazole, a first-generation PPI, was approved by the FDA in 2000 for the treatment of erosive esophagitis associated with GERD. It has been used in more than 100 different countries worldwide. It is one of the few PPIs available in multiple forms: a delayed-release oral capsule, oral suspension, and intravenous. Pantoprazole has been shown to improve acid reflux-related symptoms, heal esophagitis, and improve health-related quality of life more effectively than histamine-2 receptor antagonists. Evaluated in over 100 clinical trials, pantoprazole has an excellent safety profile, is as efficacious as other PPIs, and has a low incidence of drug interactions. It has also been shown to be safe and effective in special patient populations, such as the elderly and those with renal or moderate liver disease.

Keywords: pantoprazole, GERD, esophagitis

Introduction to gastroesophageal reflux disease

In 2006, the Montreal Consensus Group provided a global evidence-based definition of gastroesophageal reflux disease (GERD) as “a condition which develops when the reflux of stomach contents [into the esophagus] causes troublesome symptoms and/or complications”.¹ It is a chronic, often relapsing disease that if not treated appropriately can lead to further complications including esophageal ulcers, stricture formation, obstruction, Barrett’s, and esophageal cancer. In addition, GERD can potentially lead to extra-esophageal complications, such as worsening asthma-like symptoms and chest pain.² Reports indicate that GERD affects an estimated 19 million people in the US alone. This figure is likely to be an under-representation as many patients are misdiagnosed and subsequently not appropriately treated.³ Patients with GERD report a worse quality of life than those with diabetes, hypertension, mild heart failure, and angina.⁴⁻⁶

Based on the 2005 practice guidelines, the mainstay of therapy for GERD is acid suppression.⁷ Over the last 30 years, there has been an influx of various agents aimed at adequately controlling acid secretion and subsequently the symptoms of GERD. Since the discovery of the proton pump in the early 1970s and the subsequent development of proton pump inhibitors (PPIs); the mechanism by which GERD is treated has been revolutionized.⁸ In 1989, omeprazole entered the market as the first PPI to treat acid reflux.⁹ Then in 2000, pantoprazole became the fourth PPI marketed in the US and the first PPI to be available in both oral and intravenous (iv) forms.¹⁰

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Introduction of pantoprazole and its indications

After 8 years of research, Wyeth Pharmaceuticals introduced pantoprazole in April, 1985.⁸ By 1994, pantoprazole was already in use throughout Europe but Food and Drug Administration (FDA) approval for use in the US did not occur until 2000⁸ (Table 1). Initially, pantoprazole was approved for treatment and maintenance of erosive esophagitis (40 mg/day for 8 to 16 weeks).⁹ Later in 2001, pantoprazole iv was approved for short-term treatment (7 to 10 days) of GERD patients and a history of erosive esophagitis (40 mg/day) who are unable to tolerate oral pantoprazole.¹¹ Since then, the indications for pantoprazole have expanded to include a variety of gastric acid-related diseases, including peptic ulcer disease (PUD), NSAID-induced ulcer prevention, Zollinger–Ellison syndrome, and adjunctive therapy for *Helicobacter pylori* eradication.⁹

Structure and physiology of pantoprazole

Pantoprazole is a membrane permeable substituted benzimidazole derivative that decreases gastric acid secretion by irreversibly inhibiting the H⁺/K⁺-ATPase located within gastric parietal cells.^{10,12,13} It has high tissue selectivity for the canalicular lumen of the parietal cell, which has a pH of 1.¹⁴ Like other PPIs, it is a weakly basic prodrug that accumulates within this highly acidic environment and becomes rapidly activated into a cationic sulfonamide.^{10,13,15} The protonated form then covalently binds to specific cysteine residues on the H⁺/K⁺ ATPase enzyme, thus irreversibly inactivating the pump. Compared to other PPIs, pantoprazole is less likely to become activated in neutral to moderately acidic environments (pH 3 to 5). The narrow pH window prevents pantoprazole from acting at nontarget areas in the body, thus reducing adverse effects.^{10,14,16} In vitro studies have shown that pantoprazole may actually have a longer duration of action than other PPIs because it is the only PPI to bind both cysteine 813 and cysteine 882, the more distal residue of the proton pump.¹⁴ Theoretically, the distal site is less accessible

to agents such as glutathione or dithiothreitol that potentially reverse proton pump inhibition.¹⁷

Pharmacokinetics of pantoprazole

Pantoprazole follows dose linear pharmacokinetics. Oral pantoprazole has a bioavailability of 77% and its absorption is not affected by food or antacids.¹⁰ It is ultimately absorbed in the small bowel, resulting in a maximum serum concentration 2 to 3 hours postingestion.¹⁸ Therefore, pantoprazole is most effective when given prior to meals so it reaches peak serum levels when the maximum number of proton pumps are activated postprandially.¹¹ Unlike other PPIs, the serum concentration of pantoprazole is not dose-dependent; serum concentration after 1 dose is similar to that after multiple doses.¹⁹ Pantoprazole is completely metabolized via the hepatic cytochrome P450 system by CYP2C19 and CYP3A4, and up to 80% of the inactive metabolites are eliminated via renal excretion.^{11,12} The metabolism of pantoprazole is independent of the route of administration, with a half-life of approximately 1.1 hours.¹⁰ However in patients with a mutation in the gene encoding the CYP2C19 enzyme, the half-life may be up to 3 hours.²⁰

Efficacy and current findings of pantoprazole

Numerous multicenter randomized control studies have shown pantoprazole to be more efficacious than histamine-2 receptor antagonists (H2RAs) as the first-line drug for both treatment and maintenance therapy of erosive esophagitis associated with GERD.^{10,21–24} Pantoprazole 40 mg/day for 4 to 8 weeks is the optimal regimen for the treatment of moderate to severe GERD.²⁵ Patients taking oral pantoprazole 40 mg/day had higher endoscopically confirmed healing rates at 4 weeks and 8 weeks, respectively, when compared with patients taking ranitidine 150 mg twice daily (54.0% to 95.1% vs 20.0% to 66.7% and 75.0% to 98.8% vs 41.0% to 77.4%, $P < 0.001$) or nizatidine (79% vs 44%, $P < 0.001$).^{10,19,22,26,27} Similarly, patients taking pantoprazole 40 mg/day had higher endoscopic remission rates than ranitidine 150 mg twice daily

Table 1 FDA-approved indications for pantoprazole in the treatment of gastroesophageal reflux disease (GERD) in the US

Year	Indication	Dosage	Route	Duration
2000	Healing of erosive esophagitis	40 mg daily	po capsule	8–16 weeks
2000	Maintenance of erosive esophagitis	40 mg daily	po capsule	Continuous
2001	Erosive esophagitis with GERD unable to tolerate po	40 mg daily	iv	7–10 days
2007	Erosive esophagitis with GERD unable to tolerate po capsule	40 mg daily	po suspension	Continuous

Abbreviations: FAD, US Food and Drug Administration; iv, intravenous; po, by mouth.

(78.0% to 82% vs 21.0% to 33%, $P < 0.001$) for maintenance therapy at 12 months.^{14,28}

When compared to other PPIs, pantoprazole has similarly efficacy in both the initial treatment and maintenance therapy of GERD. A double-blind, randomized, control study showed that pantoprazole 40 mg/day and esomeprazole 40 mg/day produce equivalent intraesophageal pH profiles and both similarly decrease esophageal acidity to normal levels 6 to 24 hours postingestion.²⁹ Endoscopic healing rates at 4 weeks and 8 weeks show no statistically significant differences when comparing pantoprazole 40 mg/day to omeprazole 20 mg/day, omeprazole multiple unit pellet system 40 mg/day, and lansoprazole 30 mg/day.^{30–32} For maintenance therapy, pantoprazole 20 mg/day is equivalent to esomeprazole 20 mg/day for both endoscopic healing rates and symptom control at both 6 months and 12 months.^{33,34}

Pantoprazole has been shown to improve health-related quality of life more effectively than H2RAs and with similar efficacy to other PPIs.^{2,5,6,35} Patients taking pantoprazole 40 mg/day had a greater percentage of symptom-free days at 12 months compared to patients taking ranitidine 150 mg twice daily (83% vs 58%, $P < 0.001$).¹⁴ A similar study found pantoprazole to provide greater symptom relief than famotidine.²³ Although the efficacy seems to be relatively similar when comparing pantoprazole to other PPIs, limited data indicate that pantoprazole has a faster onset of symptom relief in patients with mild GERD.^{36,37} Similarly, in a study comparing pantoprazole 40 mg/day to esomeprazole 40 mg/day, patients treated with pantoprazole experienced less symptom relapse (51% vs 61%, $P < 0.05$) and fewer symptomatic episodes (56% vs 71%, $P < 0.01$) at one week post treatment than the esomeprazole group.³⁸ Pantoprazole 40 mg/day has also been shown to provide more effective control of night-time symptoms of GERD compared to esomeprazole 40 mg/day.³⁹ In the above studies, symptoms evaluated include heartburn, odynophagia, dysphagia, and acid regurgitation. Pantoprazole has positive patient satisfaction rates in trials involving patient questionnaires aimed at evaluating health-related quality of life such as ReQuest, GERDyzer, and the GERD symptom frequency questionnaire (GSFQ).^{35,40,41}

Since pantoprazole is effective in controlling symptoms related to GERD and improving health-related quality of life, interest has arisen in using pantoprazole on an as-needed basis, rather than every-day doses. This concept is known as on-demand therapy. Although not currently FDA approved, on-demand therapy with pantoprazole has been shown to be effective in the treatment of patients

with mild GERD in randomized control studies.^{42–44} In one study, patients with GERD were initially treated for 4 weeks with pantoprazole 20 mg/day, and subsequently received pantoprazole 20 mg/day or 40 mg/day for the following 6 months as needed for recurrent symptoms. A score was then calculated based on the patient's perceived average daily symptom load. At 6 months, the mean symptom load scores were significantly lower in the treatment groups than in the placebo group (pantoprazole 20 mg: 2.91; pantoprazole 40 mg: 2.71; placebo: 3.93) ($P < 0.0001$).⁴⁴ There was no statistical difference between the two dosage groups of pantoprazole. Similarly, a study ($n = 236$) of on-demand therapy for mild GERD comparing pantoprazole 20 mg to esomeprazole 20 mg revealed heartburn symptoms to be less severe in the pantoprazole group.^{42,44}

Special administration considerations of pantoprazole

Conventional pantoprazole is formulated as an enteric-coated, delayed-release tablet. However, pantoprazole is one of the few PPIs available in both iv and oral suspension form for the treatment of GERD in patients who are unable to tolerate the delayed-release capsule form.¹¹ Pantoprazole iv, which was approved in 2001 by the FDA, has equivalent efficacy to oral pantoprazole in its ability to suppress gastric acid output.⁴⁵ In 2007, the FDA also approved pantoprazole to be available in oral suspension form for the treatment of erosive esophagitis in patients unable to swallow capsules. Although studies are limited, a recent multicenter randomized control study ($N = 60$) showed oral suspension pantoprazole to provide similar efficacy to oral capsules in suppressing gastric acid output.⁴⁶

Safety and tolerability of pantoprazole

Short- and long-term clinical trials show oral pantoprazole 40 to 120 mg/day to have an excellent safety profile.⁴⁷ Studies ranging from 8 weeks to 4 years have shown the incidence of adverse effects to be as low as 1% to 3%.^{47,48} The most commonly reported side effects include diarrhea (2%), headaches (2%), nausea (1%), and constipation (1%). As with most PPIs, diarrhea is the most prevalent of these side effects.¹¹ Isolated case reports have associated pantoprazole use with thrombocytopenia and acute interstitial nephritis.^{49–51} Recently, long-term PPI use has been shown to have increased class-associated incidence for hip fractures; however, no individual reports are available for pantoprazole.⁵² Adverse side effects reported in patients with GERD who receive iv

pantoprazole include headache, nausea, dizziness, flushing, and pain at the site of injection; however, data on tolerability in this subset of patients are limited.⁵³

Randomized, controlled, double-blind control trials in patients with GERD have shown that oral pantoprazole 40 mg/day has a comparable tolerability profile to oral omeprazole 20 mg/day and lansoprazole 30 mg/day after 8 weeks of therapy.^{54,55} In addition, oral pantoprazole 40 mg/day has similar tolerability comparing to H2RAs, such as ranitidine 300 mg/day and famotidine 40 mg/day.⁵⁶ Like other PPIs, pantoprazole can cause elevated gastrin levels; however, no data have been published indicating a correlation between elevated gastrin levels and an increased risk for cancer.^{2,10}

There have been a few reported significant adverse drug interactions between pantoprazole and other medications metabolized through the CYP450 system. Unlike omeprazole, which recently has been shown to decrease the antiplatelet activity of clopidogrel, and which is also metabolized by CYP450, pantoprazole does not affect clopidogrel efficacy.⁵⁷ Given pantoprazole's lower incidence for drug interactions compared to other PPIs, it is both safe and effective for long-term treatment of acid-related disorders in the elderly, a population at increased risk for adverse interactions due to medications. In addition, older patients have a higher incidence of developing severe esophagitis and its complications. Their relapse rate is also higher than that of younger patients if therapy with a PPI is not continued. Pantoprazole is also well tolerated in patients with renal failure and mild to moderate liver dysfunction (CHILDS class A/B). However, it has a relative contraindication in patients with severe liver disease.¹¹

Conclusion and future targets

The data reviewed here show that pantoprazole is both safe and effective in the initial treatment and maintenance therapy for the management of erosive and nonerosive GERD. It has superior efficacy to H2RAs and has relatively equivalent efficacy compared to other PPIs. It is efficacious for both esophageal healing and relief of symptoms associated with GERD. Pantoprazole's favorable side effect profile and low incidence of drug–drug interactions make it ideal for using in special patient populations, such as the elderly and those with renal failure and moderate liver dysfunction. Future targets for study include more extensive trials on the use of continuous iv pantoprazole in the treatment of severe erosive esophagitis and long-term studies on the safety and efficacy of oral suspension

formulation.⁵⁸ In addition, expanding FDA approval for the use of pantoprazole in children and adolescents is currently being considered.^{59,60}

Disclosures

The authors declare no conflicts of interest.

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