

Pantoprazole in pediatric gastroesophageal reflux disease

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Proton-pump inhibitors (PPIs) are widely used in the treatment of gastroesophageal reflux disease, *Helicobacter pylori* gastritis and peptic ulcer disease. PPIs are characterized by high efficacy, safety and lack of tachyphylaxis with very selective action on the proton pump in the parietal cell. Currently, five primary PPIs are available for use in adults. Although used for similar indications in the pediatric age group, only limited data are available in children. Limited knowledge of these medications in pediatrics suggests minimal risk of short-term complications. Data are emerging on pediatric experiences with pantoprazole. Additional pharmacokinetic and clinical data are needed with this PPI, which may prove the suitability of its use in children and be used to seek pediatric labeling. A literature review of pantoprazole use in children and adolescents is presented.

Gastroesophageal reflux disease (GERD) is a condition of multifactorial etiology resulting in the reflux of gastric contents into the esophagus through the lower esophageal sphincter [1]. It is commonly diagnosed based on typical symptoms, including heartburn and acid regurgitation [2]. The manifestations and clinical presentation of GERD may vary between patients [2-4]. Patients may also present with atypical/extra-esophageal manifestations, such as asthma, hoarseness, chronic cough or noncardiac chest pain [5].

Symptoms of gastroesophageal reflux (GER) are common in children and complications associated with reflux can also occur in this age group [6]. The prevalence of GERD increases with age, from 2.5% of children between the ages of 3 and 9 years, to 8.5% of those between the ages of 10 and 17 years [7]. GERD can resolve, but may become chronic and persist into adulthood [8]. However, the natural history of GERD in childhood is not well defined, nor are the factors that predispose to Barrett's esophagus or esophageal adenocarcinoma [9]. Fewer than 50% of children diagnosed with GERD between the ages of 3.5 and 16 years have spontaneous resolution of symptoms and many require continued medical or surgical management [8].

The gastric refluxate can contain both gastric and duodenal fluids, including gastric acid, pepsin, trypsin and bile [10]. Backflow of these contents into the esophagus results in esophageal inflammation. Other factors contributing to reflux include a decrease in the lower esophageal sphincter (LES) pressure and altered motility, which can increase esophageal clearance time.

Children with GERD have abnormal, and a decreased number of, esophageal body contractions with esophageal reflux. This suggests that children with GERD with and without esophagitis have impaired esophageal body acid clearance [11]. The most important factor in the pathogenesis of GERD is the recurrent inappropriate transient lower esophageal sphincter relaxations (TLESRs) [12]. Additional factors that increase esophageal clearance time include posture-gravity interactions, size and content of a meal, abnormal gastric emptying and abnormal esophageal peristalsis [13].

Several diagnostic tests, such as extended pH monitoring, gastric scintigraphy, esophageal impedance, upper endoscopy or ultrasound, are available to detect the presence of pathologic reflux [14], however, an upper endoscopy with its ability to visualize the mucosa of the entire upper GI tract with the additional ability to obtain biopsies is considered most useful [15-17]. Furthermore, heterogeneity of GERD symptoms and findings make it difficult to define a gold-standard test. Endoscopy is the investigation of choice to diagnose reflux esophagitis, to grade its severity and to exclude other conditions that can mimic GERD, such as eosinophilic esophagitis.

Endoscopic biopsy may also facilitate the diagnosis of allergic or infectious esophageal maladies [18]. Changes such as elongation of the stromal papillae, a neutrophil infiltrate, an eosinophil infiltrate and 'balloon cells' have all been described in association with GERD in children. Histology has a major role and importance in the management of pediatric patients [19,20].

Keywords: gastroesophageal reflux disease, pantoprazole, pediatrics, proton-pump inhibitor

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Reduction of the acidity and volume of the refluxate has been considered the most effective treatment for reflux esophagitis. A threshold pH of 4.0 has been suggested during esophageal pH monitoring as a cutoff to differentiate between aggressive and nonaggressive reflux [21]. This pH was shown to be associated with the subjective onset of symptoms. Additionally, there is minimal peptic activity at pH 4.0. Acid control of the refluxate to a level of greater than 4.0 has been shown to be one of the key factors in the management of GERD [22]. This is effectively achieved by using proton-pump inhibitors (PPIs).

Proton-pump inhibitors are widely used for the treatment of GERD, as well as other acid-related disorders, such as *Helicobacter pylori* infection and gastrointestinal bleeding [23]. All available PPIs, including omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole, effectively suppress gastric acid secretion by blocking the gastric acid pump, H⁺/K⁺-adenosine triphosphatase (ATPase). They must be absorbed intact in the GI tract and enteric delivery systems are required to achieve this [24]. This review summarizes pediatric experience with pantoprazole in the management of pediatric GERD. Although useful in situations besides GERD, there is no reported pediatric experience using pantoprazole in the treatment of *H. pylori* infection or gastrointestinal bleeding.

The aims of treatment for GERD in the pediatric patient are resolution of inflammation, improvement in symptoms, maintenance of remission and prevention of complications [14]. Another important goal is to improve the quality of life in these patients. A variety of treatment options for GERD exist, including lifestyle modification, antacids, alginates, histamine 2 receptor antagonists and PPIs [2,25]. Since effective prokinetic agents that can improve the motility component of reflux are unavailable, suppression of acid production remains the best option at present [2,14,26]. Owing to their clinical efficacy, effective and prompt control of patient symptoms and reduction in the occurrence of complications and relapses, PPIs are ideal for the treatment of GERD [2,23,26].

Pantoprazole

Proton-pump inhibitors inhibit the gastric H⁺/K⁺-ATPase via covalent binding to cysteine residues of the proton pump [23,24]. All PPIs are protonated twice before complete activation, first in the parietal cell, followed by a second protonation in the secretory canaliculus. The differences between the PPIs are due to different

rates of activation, the location of covalent binding and the stability of inhibition. If bound to a deeply located cysteine residue, then the activation is slower, although its effect lasts longer. Pantoprazole is a typical example of such a PPI due to an imidazopyridine ring, which is more resistant to reversal.

Approval for pediatric use

Currently, pantoprazole is not approved for use in those less than 18 years of age in the USA. It has been approved for use in children over 12 years of age in Europe.

Pharmacokinetics

The intravenous route of administration offers a faster onset of gastric suppression with pantoprazole, achievement of intragastric pH closer to neutrality and better bioavailability. Intravenous administration of a PPI is a faster way to achieve gastric acid suppression than oral administration of the same agent [27]. Peak suppression after intravenous administration of pantoprazole occurs within hours, compared with several days later following oral administration.

Pediatric pharmacokinetic data is published as two abstracts [28,29]. These studies were to determine the pharmacokinetics of a single dose of intravenous pantoprazole in 23 hospitalized pediatric patients 1–16 years of age after informed consent. An inpatient, open-label, multiple-dose, randomized, parallel-group study was conducted in children who could benefit from acid suppression therapy. The subjects were divided into four age groups: 1–2 years, 2–4 years, 5–10 years and 11–16 years. Subjects were randomly assigned to receive either: pantoprazole 0.8 mg/kg or pantoprazole 1.6 mg/kg, infused intravenously over 15 min. Venous blood samples were collected before (0 h) and over a 12-h period after drug administration for plasma pantoprazole analysis. Gastric pH was measured 30 min before and for 24 h after drug infusion continuously. Intravenous pantoprazole was well tolerated in all age groups.

Clearance values in children aged 1–2 years were higher than those in children aged 2–4 and 5–10 years, while half-life values remained the same.

The clearance values in 2–16 year olds with different rates of metabolism were not different, suggesting the absence of the slow-metabolizer phenotype for CYP2C19. It was concluded that the pantoprazole dose for patients aged 2–16 years may be the same as that known to be efficacious in adults.

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Clinical efficacy

Pantoprazole has been efficacious in relieving the symptoms of GERD, as well as in healing and the maintenance of healing in adult patients [30–32]. A review of relevant clinical studies with pantoprazole for the management of pediatric GERD is shown in Table 1. Pantoprazole use has been reported in three pediatric studies [33–35]. Each of these studies utilized different diagnostic modalities for diagnosing GERD.

In the first trial of oral pantoprazole, a 20 mg daily dose provided gastric acid control (in 15 pediatric patients [6–13 years old] with reflux esophagitis) after 28 days of treatment [33]. Oral pantoprazole 20 mg was equivalent to 0.5–1.0 mg/kg/day in these patients with erosive reflux esophagitis. Continuous intraesophageal and intragastric pH monitoring for 24 h was performed to assess the efficacy of pantoprazole in reducing esophageal acid exposure time (pH < 4), reducing the number and duration of reflux episodes and to increase the percentage of time with gastric pH greater than 3. The intensity of five common symptoms of reflux was scored before and after treatment on a four-point scale. Esophagitis was assessed visually and by examining distal esophageal biopsies pre- and post-treatment. The median percentage of time when intraesophageal pH was less than 4 at baseline was 9.3% and decreased to 2.7% after 4 weeks of treatment with pantoprazole ($p = 0.0006$). The median percentage of time in which the intragastric pH was greater than 3 also increased from 21% at baseline to 39% at the end of treatment ($p = 0.005$). All patients had some improvement in reflux symptoms after 4 weeks of treatment. Although esophagitis was healed in 47% of children at repeat endoscopy, biopsies were still abnormal.

Symptom improvement was evaluated in 53 children (aged 5–11 years) with endoscopically proven GERD treated with pantoprazole

10, 20 and 40 mg [34]. Of the 53 patients randomly assigned to receive pantoprazole, four had erosive esophagitis and 49 had nonerosive GERD. Of those with erosive esophagitis (Hetzel-Dent scores \geq grade 2 at baseline), three patients were in the 20 mg treatment group and one patient was in the 40 mg treatment group. The GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q) was used to assess the efficacy of treatment [36]. This GASP-Q was used to monitor the GERD symptoms of abdominal/belly pain, chest pain/heartburn, difficulty swallowing, nausea, vomiting/regurgitation, burping/belching and choking with eating and postprandially over the previous 7 days. The frequency and severity of each symptom determined individual symptom score (ISS). The individual symptom scores were added to determine the composite symptom score (CSS).

The change in the mean CSS from baseline to week 8 determined the primary outcome. Mean frequency and severity of each symptom significantly decreased (from $p < 0.006$ to $p < 0.001$) during the study. Similar significant decreases in CSS at week 8 versus baseline ($p < 0.001$) were seen in all dose groups. CSS significantly decreased from baseline to week 8 in the 20 ($p < 0.003$) and 40 mg ($p < 0.001$) groups. The 20 and 40 mg doses were significantly ($p < 0.05$) more effective than the 10 mg dose in improving GERD symptoms at week 1. Adverse events were similar among the treatment groups. Both 20 and 40 mg doses of pantoprazole significantly reduced symptoms by the first week of the study. Pantoprazole (20 and 40 mg) was effective in reducing endoscopically proven GERD symptoms in this cohort of children. All patients with erosive esophagitis had a score of 0 (normal) or 1, and were healed by the end of the study.

Table 1. Pediatric pantoprazole studies in children with gastroesophageal reflux disease.

Author	No. of Patients	Age (years)	Daily dose (mg/d)	Duration of treatment (weeks)	Outcome	Ref.
Madrazo-de la Garza <i>et al.</i> (2003)	15	6–13	20	4	Symptom improvement, healing of esophagitis in 47% of children and improved pH monitoring	[33]
Tolia <i>et al.</i> (2006)	4 erosive 49 nonerosive	5–11	10, 20 or 40	8	Symptom improvement in all groups – best in 20 and 40 mg group – and healing of erosive esophagitis in all	[34]
Tsou <i>et al.</i> (2006)	136	12–16	20 or 40	8	Symptom improvement in both groups	[35]

A multicenter study to evaluate the efficacy of pantoprazole treatment was conducted in 136 adolescents aged 12–16 years [35]. An age-appropriate GASP-Q was used to assess the frequency and severity of the GERD symptoms, which included abdominal/belly pain, chest pain/heartburn, pain after eating, nausea, burping/belching, vomiting/regurgitation, choking when eating and difficulty swallowing. The mean CSS at baseline and week 8 was compared after treatment with 20 or 40 mg of pantoprazole. The dose range of pantoprazole used was 0.3–0.9 mg/kg, except in five patients who received greater than 0.9 mg/kg in the 40 mg dose cohort. Significant improvement in CSS occurred in both groups ($p < 0.001$).

Safety & tolerability

Overall, the limited published experiences with pantoprazole in pediatric studies suggest that it is efficacious and well tolerated. Its adverse events profile is very similar to that in adults. The median serum gastrin level increased slightly within the reference range during this 4-week course of treatment in one study. In one patient there was a transient elevation of serum aspartate aminotransferase and alanine aminotransferase during treatment. It was safe and well tolerated [33]. Most treatment-associated adverse events have been mild to moderate in severity and include headache, nausea, abdominal pain, increased appetite, dizziness, insomnia and urinary incontinence [34]. Similar adverse events of headache, diarrhea, abdominal pain, infection and pharyngitis were noted in the larger clinical study by Tsou *et al.* [35]. Incidence of headache led to withdrawal from the study in three patients and diarrhea in seven patients. Overall, safety was comparable between the two dosage groups of 0.3 mg/kg and 0.3–0.9 mg/kg. Pantoprazole was safe, well tolerated and effective in reducing the symptoms of GERD in adolescents [35].

Review of available studies demonstrated that pantoprazole therapy once daily for 8 weeks provided a high healing rate in the small number of children and adolescents with erosive esophagitis (95–100% rate of healing) and a significant reduction in GERD-related symptoms in the rest of the patients with GERD symptoms [34].

Conclusions

Among children and adolescents, GERD is a significant source of morbidity. Increasing evidence supports the theory that reflux disease originates in childhood [37,38]. A recent prospective study of

54 children between the ages of 6 and 17 years (mean age: 10.3 years) revealed that 39% had a history of reflux disease during infancy [39].

Complications of GERD, such as erosive esophagitis, stricture, hemorrhage and Barrett's esophagus were believed to occur infrequently in children. However, such complications are being increasingly diagnosed in both children and adolescents [40]. Although the natural history of gastroesophageal reflux-related mucosal disease is not as well characterized in children and adolescents as it is in adults, a large study of 402 neurologically normal children with GERD who were free of other comorbidities, found that more than 33% had complications, such as erosive esophagitis [6]. Another prospective study in children found no correlation between endoscopic grade of esophagitis and symptoms of gastroesophageal reflux. Among the 54 children with symptoms of reflux, 83% had grade I and 17% had grade II esophagitis [39]. Tolia *et al.* found that symptoms of gastroesophageal reflux produce significant decreases in quality of life for the child with reflux, as well as the parents [41]. The morbidity, long-term complications and economic burden of gastroesophageal reflux in adults make it easy to infer that early detection and effective treatment during childhood may result in a better long-term outcome. However, the management of children and adolescents with gastrointestinal diseases is different from adults as issues unique to this age group, such as growth, side effects, quality of life and psychosocial factors, need to be addressed.

Additional studies in patients younger than 5 years of age are underway with appropriate formulations of pantoprazole to evaluate safety and efficacy in this younger age cohort. Although the data on the long-term safety of pantoprazole in the management of pediatric patients is limited [42], short-term therapy of 8–12 weeks appears to be an effective therapeutic modality in children and adolescents with GERD between 5 and 17 years of age.

Future perspective

Gastroesophageal reflux disease is frequently experienced by infants and children. There is preliminary evidence to suggest that pantoprazole may be an acceptable choice of treatment in improving symptoms in symptomatic pediatric patients between 5 and 17 years of age. The medication needs to be studied in younger patients with formulations that are pharmacodynamically equivalent to tablets, safe and well tolerated.

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Pediatric patients with GERD who are unable to swallow the tablet need to be treated with alternative pantoprazole sodium preparations, such as granules in suspension. Further research to assess the genetic polymorphism of CYP2C19 and the impact of ontogeny on the activity of this and other enzymes (e.g., CYP3A4) should be conducted. These may affect the biotransformation of the PPIs and, thus, their plasma clearance. In addition, the potential effects of different formulations of the drug on their rate and extent of absorption must be considered. Because of the apparent safety of

PPIs and a possible response in patients with GERD, it is possible that their use in pediatric practice will increase.

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Executive summary

- Pantoprazole has been studied for treatment of gastroesophageal reflux disease (GERD) in children and adolescents between 5 and 17 years of age.
- Pantoprazole was shown to be effective in improving clinical symptoms of GERD at different dosages in these age group cohorts.
- Pantoprazole has also been shown to improve symptoms of endoscopically diagnosed GERD over 8 weeks of treatment compared with baseline, however, higher doses of 20 and 40 mg/day improved symptoms by 1 week of treatment.
- Its adverse effect profile in pediatrics was similar to that described in the package insert.
- Additional studies are ongoing in children less than 5 years of age and in infants to assess efficacy and safety with appropriate formulations for these age groups.

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