Review of pantoprazole in pediatrics

This article summarizes the effect of pantoprazole, a proton pump inhibitor (PPI) on suspected or objectively demonstrated gastroesophageal reflux disease (GERD) symptoms in pediatric age range from premature infants to 16 years of age. All interventional studies in English language are reviewed including pharmacokinetic and pharmacodynamic reports. Oral pantoprazole was evaluated in preterm infants, neonates, infants, children and adolescents in multiple trials designed to meet US FDA requirements. Its PK and PD profile has been reported for both oral and intravenous routes. Its disposition was similar to that in adults and showed no evidence of accumulation when repeated doses were studied. In CYP2C19 and CYP3A4 slow metabolizers, the half-life was prolonged; however, data on pharmacogenomics is limited. Its adverse effect profile was similar to that in adults. It was efficacious in resolving gastroesophageal reflux (GER) symptoms partially or completely in 1–16-year-old subjects and in healing erosive esophagitis, however, it has been approved for treating GERD in patients between the ages of 5–16 years for up to 8 weeks only. It was not effective in treating infants under 1 year of age with symptoms suggestive of GERD and because of unavailability of formulation appropriate for children younger than 5 years; it is not approved for use under this age. Further studies are needed to expand the understanding of pantoprazole treatment in infants.

KEYWORDS: adolescents ■ children ■ efficacy ■ gastroesophageal reflux disease ■ infants ■ pantoprazole ■ safety

Vasundhara Tolia

Michigan State University College of Human Medicine, A110 East Fee Hall East Lansing, MI 48824-1316, USA
Tel.: +1 248 647 3243
Fax: +1 248 647 2227
vasu.tolia@gmail.com

Gastroesophageal reflux (GER) is occasionally experienced by almost everyone post-prandially and is a normal physiologic phenomenon under such circumstances. However, when it occurs frequently causing either bothersome symptoms or damage to esophageal mucosa, it is called gastroesophageal reflux disease (GERD) [1]. Under these situations, it can cause other complications and/or involve extra-esophageal organs [2]. The single most common cause of GERD is inappropriate transient lower esophageal sphincter relaxation; called (TLESR); which allows backflow of gastric contents into the esophagus. Although GERD can occur without any underlying predisposing factors; it can be due to other coexisting conditions such as esophago-gastric dysmotility, anatomic abnormalities of the esophagus (e.g., tracheoesophageal fistula or developmental delay) [3]. Then it is called secondary GERD. GERD frequently coexists with obesity. Whether primary or secondary in nature, when GER causes troublesome symptoms and affects the quality of life in an individual, it becomes GERD and needs to be treated. Fortunately, some of the GERD complications observed in adults such as Barrett's esophagus and accompanying mucosal dysplasia are infrequent in childhood.

Clinical presentation

Gastroesophageal reflux disease can present at any age in otherwise healthy children and has a wide range of symptoms which can vary at different ages [3]. A good history is usually adequate to suggest presence of GERD. Infants can present with crying and/or unexplained irritability, apnea and/or bradycardia, acute life-threatening event, poor appetite or feeding refusal, recurrent vomiting or stridor. In severe cases, persistent emesis can cause actual weight loss or failure to thrive [4]. Older children can present with recurrent spitting/vomiting, burping/belching, epigastric abdominal pain, chest pain or even heartburn. Atypical manifestations of GER involving respiratory, otolaryngologic and dental regions include wheezing, stridor, hoarseness, chronic cough, dental erosions and recurrent sinusitis/otitis [3]. Rarely, erosive GERD can manifest with torticollis type of picture called Sandifer's syndrome. Dietary habits, alcohol intake and exposure to active or passive smoking should also be part of the clinical assessment.

There are no classic physical signs for diagnosing GER in the pediatric population. In most cases, diagnosis can be suspected from the history and a normal physical examination. Empiric conservative management can be

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usually initiated without any diagnostic tests. Albeit, if extra-esophageal symptoms are present or if the patient does not respond to treatment; investigations should be performed to exclude other conditions.

Management

Lifestyle modifications are the mainstay of GERD management. These include small volume, frequent feedings, thickening of formula, holding the baby upright after feeding and perhaps consider even an empiric trial of hypoallergenic formula in infancy. In children and adolescents, smaller meals with avoidance of fried, fatty foods, acidic products, peppermint, chocolate and caffeine-containing foods and beverages should be suggested [3]. Abstinence of alcohol and tobacco is prudent. Proper eating habits with consideration of weight-holding or weight-losing diet should be discussed with the family as indicated tactfully. If the patient does not respond to these conservative measures, then pharmacotherapy is indicated [3]. It is important to remember that lifestyle changes should continue to be encouraged even in the presence of medications.

Although acid reflux is a major player in the etiology of GERD, other factors including decreased lower esophageal sphincter pressure, TLESRs, esophageal and gastric dysmotility can also contribute towards GERD as mentioned previously [5]. Since effective medications to modify latter factors are not available, pharmacologic management of GERD is currently focused on acid suppression.

North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for management of GERD recommend the use of 'step-up' and 'step-down' therapy under the supervision of a pediatric gastroenterologist [3]. 'Step-up' therapy means progressing from milder acid suppression medications such as H_2 receptor antagonists (e.g., ranitidine, nizatidine, famotidine or cimetidine) to proton pump inhibitors (PPIs). 'Step-down' approach involves starting with more potent medications such as PPIs initially and then weaning to milder medications after improvement. Five PPIs are available for the management of GERD including omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. Although all of these have been approved for pediatric use for the short-term management of GERD, age range of US FDA approval varies. This article will focus on the use of pantoprazole in the pediatric population.

Previously, data from adult studies were extrapolated to assess pediatric dosages and efficacy. However, such generalizations from adult data is not always accurate or safe for infants and children [6]. Since the mandate of performing pediatric studies, a white paper demarcating specifics of age groups, doses and study characteristics was issued by the FDA for evaluating safety and efficacy of pantoprazole in the pediatric age group. Most published pantoprazole studies have been conducted to fulfill these criteria in subjects ranging in age from premature babies and neonates to 16 years [101]. A pediatric granule formulation was studied in children under 5 years of age, and pantoprazole delayed-release tablets were studied in children older than 5 years. A few pharmacokinetic (PK) and pharmacodynamic (PD) studies have also been performed. Based on the safety and efficacy data from these studies, pantoprazole has been approved by the FDA for use in patients aged 5–17 years for up to 8 weeks for treatment of GERD in the USA. The safety and effectiveness of pantoprazole treatment up to 8 weeks for erosive esophagitis (EE) due to GERD has been established in pediatric patients 1 year through 16 years of age. However, since an age-appropriate dosage formulation for patients less than 5 years of age is not available; pantoprazole is only indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of pantoprazole for pediatric uses other than GERD and EE have not been established.

Pantoprazole

Pantoprazole sodium sesquihydrate, 5 (difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, monosodium salt, is also called pantoprazole or pantoprazole sodium. A substituted benzimidazole derivative, it is a potent, acid-activated, irreversible inhibitor of the H^+/K^+-ATPase of parietal cells and produces prolonged suppression of gastric acid secretion [101]. Intravenous and oral formulations of pantoprazole sodium have been marketed as PROTONIX® (Wyeth Pharmaceuticals) worldwide. Pantoprazole blocks the final step of gastric acid secretion by covalently binding above enzyme system at the luminal aspect of the gastric parietal cell. Both the basal and stimulated gastric acid secretion are inhibited by its action. Its antisecretory effect lasts over 24 h for doses of pantoprazole varying from 20 to 120 mg in adults. While many studies have been reported demonstrating safety and

efficacy in adults with erosive and nonerosive GERD, available pediatric literature has been reviewed in this article.

Pediatric studies

All published pediatric studies in English are summarized in TABLE 1 and briefly discussed below. The clinical efficacy and safety studies have varied in duration from 4–8 weeks, where as PK and efficacy studies have lasted from 5 days to 6 weeks.

The earliest pediatric study to assess the efficacy and safety of oral pantoprazole was reported from Mexico [7]. A total of 15 pediatric patients (6 to 13 years old, 9 boys) with GERD were treated with 20 mg pantoprazole (0.5–1.0 mg/kg/day) once daily for 4 weeks. PD efficacy of pantoprazole to decrease esophageal acid reflux was assessed by continuous intragastric and intraesophageal pH monitoring for 24 h. Intraesophageal pH <4, the number and duration of reflux episodes, and change in the percentage of time with gastric pH >3 was assessed along with the change in five reflux symptoms before and after treatment. Endoscopic changes in reflux esophagitis were recorded at baseline and after treatment visually and biopsies from the distal esophagus were reviewed. After 4 weeks of pantoprazole treatment, pH monitoring revealed significant improvement in esophageal acid exposure parameters. Furthermore, percentage of time with intragastric pH >3 increased from 21% at baseline to 39% on day 28 of therapy ($p = 0.005$). Reflux symptoms also improved partially or completely in all patients. Repeat endoscopy showed visual healing of esophagitis in 47% of children; however, histologic healing was not achieved by 4 weeks. Expected increase in median serum gastrin levels over baseline levels (from 74 to 93 pg/ml) did occur. Transient increase in serum AST and ALT occurred in one patient during the course of treatment. Overall, pantoprazole was safe and well tolerated.

The rest of the published studies with oral pantoprazole were conducted to fulfill FDA requirements [101]. Tolia and associates evaluated the effect of pantoprazole (10, 20 and 40 mg) using the GERD Assessment of Symptoms in Pediatrics Questionnaire(GASP-Q) in 53 children (aged 5–11 years) with endoscopically proven GERD [8]. Individual symptom scores were recorded based on the frequency and severity of the following symptoms over the previous 7 days: abdominal/belly pain, chest pain/heartburn, difficulty swallowing, nausea, vomiting/regurgitation, burping/belching, choking when eating and pain after eating. A composite symptom score (CSS) was derived from the individual symptom score values [9]. The change in the mean CSS pre and post 8 weeks of therapy was compared. Mean frequency and severity of individual symptom significantly decreased (from $p < 0.006$ to $p < 0.001$) over 4 weeks. As expected, CSS also significantly improved at completion of 8 weeks compared to baseline levels ($p < 0.001$). The 20 and 40 mg doses were noted to be significantly ($p < 0.05$) more effective than the 10 mg dose in improving GERD symptoms at the end of the first week of treatment suggesting a faster resolution of symptoms with higher doses. Adverse events were similar among all the dose groups.

Tsou *et al.* evaluated the efficacy and safety of 20 or 40 mg of pantoprazole administered daily in adolescents aged 12 to 16 years [10]. An age-appropriate questionnaire (GASP-Q) was used to assess the frequency and severity of the same symptoms suggestive of GERD as described in the Tolia study [8]. A mean CSS from pretreatment to study completion at week 8 was compared after treatment with 20 or 40 mg of pantoprazole. CSS significantly improved ($p < 0.001$) in both dose groups with a similar safety profile. Pantoprazole safely and effectively improved GERD symptoms in this study in adolescents.

A multicenter, randomized, double-blind (DB) study was performed in subjects aged 1–5 years to evaluate the efficacy and safety of three doses of delayed-release oral suspension (granules) of pantoprazole by Baker *et al.* [11]. The medication was administered at low dose (LD; 0.3 mg/kg), medium dose (MD; 0.6 mg/kg), and high dose (HD; 1.2 mg/kg) for 8 weeks. All had symptomatic GERD as well as either endoscopically proven EE secondary to reflux or histologic evidence of esophagitis suggestive of GERD. While 54 patients with histologic esophagitis (HE) were randomized to LD, MD or HD pantoprazole, four with EE were assigned to MD or HD of medication only. The GERD symptoms were monitored by an eDiary filled by parents. Daily symptom scores were tabulated to derive mean weekly GERD symptom score. This weekly GERD symptom score (WGSS) was analyzed for the modified intention-to-treat HE population at 8 weeks. The score improved significantly for two of the doses (LD, HD); with LD ($p < 0.001$), MD ($p = 0.063$), and HD ($p < 0.001$) by paired t-tests. There was no significant difference between the doses regarding symptom control. All four patients with EE were healed at the end of the study. Adverse events were similar for all doses.

Table 1. Pediatric pantoprazole studies.

Author	Type of study	Number of patients in the study (M:F)	Age range	How diagnosed	Pantoprazole dose	Duration of treatment	Pre- and post-intervention assessment	Outcome	Ref.
Kierkus *et al.*	OL, PD	16 (12:9)	Preterm and neonates <28 days postnatally	Clinically	1.2 mg/kg	>5 days	Clinical and IE and IG pH monitoring	Normalized IE AUC and IG pH and AUC	[28]
Kierkus *et al.*	OL, PD	24 (12:12)	Infants from 1 to 11 months	Clinically	0.6 mg/kg in 12 patients 1.2 mg/kg in 12 patients	>5 days	Clinical and IE and IG pH monitoring	Normalized IE AUC and IG pH and AUC with higher dose	[28]
Winter *et al.*	OL x 4 weeks followed by R,DB, PC withdrawal phase x 4 weeks	128 in OL 106 in modified DB ITT phase	Infants from 1 to 11 months	Clinically	5 mg/day for 2.5 to <7 kg weight; 10 mg/day for >7 kg to <15 kg	4 weeks OL phase	Weekly GERD symptom scores	Significant symptom improvement in OL phase; similar symptom scores in both groups in DB phase – a few symptoms worse with placebo at 5 weeks	[12]
Baker *et al.*	R, DB, multidose, parallel group	60	>1–5 years	Clinically with GSQ-YC questionnaire with EGD and biopsy	0.3, 0.6 or 1.2 mg/kg in 1:1:1 fashion	8 weeks	GSQ-YC and EGD with biopsy	Significant improvement in symptom score with LD and HD. Healing of erosive esophagitis	[11]
Tolia *et al.*	R, DB, multidose, parallel group	53	5–11 years	Clinically with GASP-Q and EGD with biopsy	10 mg/day in 19 patients, 20 mg/day in 19 patients 40 mg/day in 16 patients	8 weeks	GASP-Q and EGD with biopsy	Clinical improvement with all doses at 8 weeks, with higher efficacy in 20 and 40 mg groups	[8]
Tsou *et al.*	R, OL, 2 doses, parallel group	136	12–16 years	Clinically with GERD symptom score	20 mg/day or 40 mg/day	8 weeks	Clinically with GERD symptom score	Significant symptom improvement in both dose groups	[10]
Madrazo-de la Garza *et al.*	OL	15	6–13 years	EPM and/or EGD with biopsy	20 mg/day	4 weeks	Clinically, EPM and EGD with biopsy	Significant symptom and EPM parameters improvement; 47% had endoscopic healing at 4 weeks	[7]

AUC: Area under curve; DB: Double blind; EGD: Esophago-gastro-duodenoscopy; GASP-Q: GERD Assessment of Symptoms in Pediatrics Questionnaire; GERD: Gastroesophageal reflux disease; GSQ-YC: GERD Symptom Assessment Questionnaire for Young Children; HD: High dose; IE: Intra-esophageal; IG: Intragastric; ITT: Intention to treat ; LD: Low dose; OL: Open label; PC: Placebo controlled; PD: Pharmacodynamic; R: Randomized.

The efficacy of pantoprazole in infants with clinically diagnosed GERD was assessed in 128 infants aged 1 through to 11 months (mean age 5.1 months [82% full-term, 64% male]) after not responding to 2 weeks of conservative, nonpharmacologic treatment [12]. Those with ongoing symptoms received open-label (OL) pantoprazole 1.2 mg/kg/day for 4 weeks. This was followed by a 4-week randomized, DB, placebo-controlled, withdrawal phase. The primary end point was lack of efficacy in the DB phase leading to termination from the study. Daily assessments of five GERD symptoms (vomiting/regurgitation, choking/gagging, back arching, irritability/fussiness and feeding refusal) were compiled into mean WGSSs. Safety was also monitored. Of the 128 patients in the OL phase of treatment, 106 entered the DB phase and were randomized equally to receive treatment with the same dose of pantoprazole or placebo for an additional 4 weeks. Although WGSSs decreased significantly from baseline during OL therapy with pantoprazole ($p < 0.001$), this improvement continued during the DB phase in both arms of the study. The withdrawal rate due to lack of efficacy in both groups (pantoprazole 6/52; placebo 6/54) was similar as was the time to withdrawal during the DB phase. However, WGSS was slightly worse with placebo at week 5 ($p = 0.09$) for the symptom of back arching ($p = 0.028$). Although pantoprazole significantly improved GERD symptom scores, there were no significant differences between pantoprazole and placebo groups during the DB treatment phase, or in withdrawal rates between the groups showing lack of efficacy. There were no serious treatment related adverse events. In this trial, the adverse reactions of elevated CK, otitis media, rhinitis and laryngitis were reported more commonly (difference of ≥4%) in the treatment arm compared to the placebo arm of the study group. Because pantoprazole was not shown to be effective in this randomized, placebo-controlled study in this age group, the use of pantoprazole for the treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Previous studies evaluating other PPIs in infants less than 1 year of age with suspected or proven GERD, provided limited or unsatisfactory evidence of therapeutic efficacy of PPIs in this age group [13–19]. Lansoprazole was administered at a dose of 0.5 or 1.0 mg/kg/day to neonates or 1.0 or 2.0 mg/kg/day to infants in a 5-day OL study. It increased intragastric pH and reduced vomiting/regurgitation episodes in infants younger than 1 year with symptomatic GERD [13]. In another study, lansoprazole administered 15 mg once daily or 7.5 mg twice daily for 2 weeks decreased GERD-related symptoms from baseline with revised Infant Gastroesophageal Reflux Questionnaire scores [14]. A dose-finding study was conducted in children under 2 years of age (range: 1.25–20 months) with omeprazole. It was administered at a dose of 0.7 mg/kg/day and was effective in improving the reflux index after at least 1 week of treatment [15]. In a PD and systemic exposure study in preterm and term infants with GERD, the total number of symptomatic reflux episodes were reduced along with improvement in symptoms of gagging and irritability significantly ($p < 0.05$) after 1 week of therapy with esomeprazole in the dose of 0.5 mg/kg once daily in comparison to baseline [16]. Placebo-controlled studies with PPIs in infants with GERD have not demonstrated a significant therapeutic benefit of these medications. A single-blind, randomized, placebo-controlled, dose-withdrawal study of esomeprazole 0.25 mg/kg or 1 mg/kg for 7 days reported good tolerance and dose-related acid suppression in patients with GERD aged 1–24 months [17]. Although this dose withdrawal study showed that patients treated with esomeprazole had a 31% reduced risk of discontinuing from the study due to worsening of symptoms compared with infants who received placebo; these benefits did not translate into a statistically significant difference between the treatment groups in the DB phase. Esomeprazole was well tolerated in this infant population with a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD.

Furthermore, in a DB, randomized, placebo-controlled study with lansoprazole in 162 infants aged 1–12 months, the frequency of various GERD symptoms was similar in patients treated with lansoprazole (0.2–0.3 mg/kg/day for infants 10 weeks or younger or 1.0–1.5 mg/kg/day for infants older than 10 weeks) for 4 weeks and in patients receiving placebo [18]. In addition, the percentage of patients with at least a 50% reduction from baseline in the percentage of feedings with crying episodes or the duration of crying episodes averaged across feedings was similar after treatment with lansoprazole compared with placebo [18].

The safety of PPI treatment is of concern in this infant population [19,20]. Young infants with immature immune systems may be more susceptible to infections [21]. Lower and upper respiratory infections were more frequent in patients treated with lansoprazole (4/81 patients

and 1/81 patients, respectively) versus placebo (1/81 patients and 0/81 patients, respectively). This difference was not statistically significant [18]. However, in the pantoprazole study by Winter *et al.* [12], the incidence of upper respiratory infections was similar between patients withdrawn in both pantoprazole (7/54 patients) and placebo (7/54 patients) arms. In the esomeprazole study also, there was a nonsignificant increase in the incidence of upper respiratory infection in patients treated with esomeprazole (6/39 patients) compared with placebo (4/41 patients) [17].

These pediatric trials were not performed with placebo, active comparator or in a dose response manner, so the clinical benefit of pantoprazole for symptomatic GERD in the pediatric population remains inconclusive [8,10–12]. Placebo controlled trials are very difficult to conduct in pediatric age patients owing to poor acceptance by parents, investigators and regulatory boards. Although the trial of pantoprazole for the short-term treatment of EE due to GERD in pediatric patients aged 1 to 5 years suggested efficacy and safety, lack of a commercially available, age-appropriate dosage formulation in this age group may also have played a role in not receiving FDA approval in this age group. Resolution or improvement of EE in pediatric patients with GERD has also been reported with placebo, H_2RAs and other PPIs administered orally [3,22–26].

Pharmacokinetics

While the use of PPIs in the pediatric population has risen sharply within the past 5 years, there is still little known about their PK and PD profiles in children. Age-appropriate dosing for using pantoprazole can only be obtained by properly understanding this drug's PK profile in children. Hence, several PK studies have been conducted in the pediatric age group. Both oral and intravenous PK studies are summarized in Table 2.

The PK profile of single and multiple doses of pantoprazole delayed-release tablets was characterized in 24 children aged 6–11 years and in 22 adolescents between 12 and 16 years old with GERD by Ward *et al.* [27]. Patients received 20 or 40 mg of pantoprazole once daily by a random assignment. Serial pantoprazole concentrations were measured over 12 h after the first dose and at 2 and 4 h after repeated doses on the 5th day to assess PK data by standard noncompartmental methods. Pantoprazole PK was dose independent with normalized dose. Since results were similar to PK reported from adult studies, a 20 or 40 mg tablet can be used in 6–16-year-old children with GERD. There was no evidence of accumulation with multiple dosing or evidence of serious drug-associated adverse events during safety monitoring.

The PD response to pantoprazole in infants with GERD was evaluated in two OL studies to determine dose recommendation by monitoring efficacy [28]. An OL study was conducted in 21 neonates and preterm infants using 1.2 mg/kg of pantoprazole once daily by Kierkus and associates. Patients were stratified into two groups by age. A total of 24 additional infants aged between 1 and 11 months were treated with 0.6/kg (LD) or 1.2 mg/kg (HD) of pantoprazole once daily formed another group in this OL study. Extended intraesophageal and intragastric pH-metry parameters were compared between baseline and steady state after receiving pantoprazole for ≥5 days. Treatment lasted up to ≤6 weeks. In both groups, the high dose provided similar and significant improvements in all pH-metry parameters including increase in mean gastric pH and percentage time gastric pH >4 ($p < 0.05$ both studies), normalized area under the curve (AUC) of gastric pH ($p < 0.05$ for infant study), and normalized AUC of esophageal pH ($p < 0.05$ both studies). The AUC of esophageal pH <4 decreased. Although AUC of esophageal pH decreased ($p < 0.05$ both studies) suggesting increased pH of refluxate, there was no significant change in mean esophageal pH or reflux index. The AUC measurement of esophageal pH has been previously reported as a more sensitive measure of changes in esophageal pH [29]. High-dose pantoprazole improved pH-metry parameters after ≥5 consecutive days, and was safe for ≤6 weeks in neonates, preterm infants, and infants aged 1–11 months. No accumulation of pantoprazole occurred following multiple doses. Pantoprazole granule use was safe and well tolerated in preterm infants and neonates, however, mean exposures with 2.5 mg of pantoprazole were slightly higher than that in adults with the 40 mg dose. Although the half-life was longer, there was no accumulation.

In a population PK analysis of single and multiple doses of pantoprazole by Ward *et al.* [30], the systemic exposure was higher in patients under 1 year of age with GERD compared to adults who received a single 40 mg dose (geometric mean AUC was 103% higher in preterm infants and neonates receiving a single dose of 2.5 mg of pantoprazole, and 23% higher in infants 1 through to 11 months of age receiving a single dose of approximately 1.2 mg/kg) [26]. In these

Table 2. Pediatric pantoprazole pharmacokinetic studies.

Author	Type of PK study	Age range	Number of patients	Route of administration	Dose of pantoprazole	Number of doses	Results	Ref.
Ward *et al.*	Population	Preterm infants and neonates	40	Oral	1.25 mg in 19 patients; 2.5 mg in 21 patients	Single dose in 40 patients; multiple doses in 39 patients	Concentrations variable after single and multiple doses; no accumulation after both multiple doses; mean exposure with pantoprazole 2.5 mg was slightly higher compared with adults with 40 mg	[30]
Ward *et al.*	R, OL	6–11 years 12–16 years	24 22	Oral Oral	20 mg in 11 and 40 mg in 13; 20 mg and 40 mg in 11 patients each	Single and multiple doses	Pantoprazole PK was dose independent and similar to adults; no evidence of accumulation after multiple doses	[27]
Pettersen *et al.*	OL, Phase I/II, population	10 days–16.4 years	20	Intravenous	20 mg/1.73 m^2/day in neonates; 40 mg/1.73 m^2/day in >1 month old		PK in ICU patients variable based on SIRS, hepatic dysfunction and concomitant drugs	[35]
Ferron *et al.*	OL	2–16 years	14	Intravenous	0.8–1.0 mg/kg	Single dose over 15 min	Pantoprazole PK similar to adults	[34]
Kearns *et al.*	OL	5–16 years 2–26 years	16 24	Oral Intravenous	20 mg or 40 mg 0.8–1.0 mg/kg	Single Single	Pantoprazole PK was dose dependent and similar to adults in both oral and iv. groups	[31]

ICU: Intensive care unit; iv.: Intravenous; OL: Open label; PK: Pharmacokinetics; R: Randomized; SIRS: Systemic inflammatory response syndrome.

patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 l/h, range: 0.03 to 3.2 l/h). These doses resulted in higher gastric but not esophageal pH. Following once-daily dosing of 2.5 mg of pantoprazole in preterm infants and neonates, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at steady state) and in the mean percentage time that gastric pH was >4 (from 60% at baseline to 80% at steady state). Following once-daily dosing of approximately 1.2 mg/kg of pantoprazole in infants 1 through to 11 months of age, there was an increase in the mean gastric pH (from 3.1 at baseline to 4.2 at steady state) and in the mean percentage time that gastric pH was >4 (from 32% at baseline to 60% at steady state). However, no significant changes were observed in mean intraesophageal pH or percentage time that esophageal pH <4 in either age group. In this population PK analysis, total clearance increased with increasing bodyweight in a nonlinear fashion. The total clearance also increased with increasing age only in children under 3 years of age.

In a population PK analysis, clearance values of pantoprazole in children aged 1–5 years old with endoscopically proven GERD had a median value of 2.4 l/h. The plasma concentrations of pantoprazole were highly variable and the median time to peak plasma concentration was 3–6 h after a dose approximating up to 1.2 mg/kg (15 mg for ≤12.5 kg and 20 mg for >12.5 to <25 kg). The estimated AUC for patients 1–5 years old was 37% higher than for adults receiving a single 40 mg tablet, with a geometric mean AUC value of 6.8 µg h/ml [31].

Kearns and colleagues conducted two OL, single-dose PK studies of pantoprazole in children between 2 and 16 years of age [32]. In the first study, 24 children were randomized to receive a single oral dose of either 20 or 40 mg pantoprazole after an 8 h fast. In the second study, 19 patients were stratified by age (2–4 years, 5–10 years and 11–16 years). All patients received a single intravenous dose of either 0.8 or 1.6 mg/kg pantoprazole (maximum dose 80 mg) infused over 15 min. The mean maximum plasma concentration was 2.97 ± 1.51 mg/l after oral pantoprazole. The maximum plasma concentration with the 1.6 mg/kg intravenous dose was higher than the 0.8 mg/kg dose (10.3 ± 3.7 mg/l vs 5.7 ± 2.7 mg/l; $p < 0.05$), demonstrating dose linearity similar to earlier adult studies. Clearance was similar in the oral and intravenous studies, with a mean rate of 0.26 ± 0.20 l/h/kg in the oral study and 0.20 ± 0.23 l/h/kg in the intravenous study. Mean elimination half-life was 1.27 ± 1.29 h after oral dosing and 1.22 ± 0.68 h after intravenous dosing. As anticipated, children known to be CYP2C19-extensive metabolizers had significantly lower plasma pantoprazole concentrations and a more rapid clearance than the children who were poor metabolizers. The results of this study suggest that the PK profile of pantoprazole in children is similar to that of adults and does not appear to vary with growth above the age of 2 years. The doses used in the study were well tolerated; however, additional clinical trials with pantoprazole in the treatment of children with gastroesophageal reflux are warranted.

In summary, these findings suggest that the PK of pantoprazole in children aged 1–11 years are dose dependent under certain conditions. The overall exposure of pantoprazole achieved after a single dose of 5–10 mg in children aged 1–6 years and 10–20 mg in children aged 5–11 years was comparable with exposure reported in single-dose studies of adolescents and adults.

Pharmacogenomics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., ~3% of Caucasians and African–Americans and 17–23% of Asians are poor metabolizers). In Ward's study, cytochrome P450 2C19 (CYP2C19) and CYP3A4 genotypes were determined [30]. Two patients with the CYP2C19 poor metabolizer genotype had a substantially higher AUC than extensive metabolizers. Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a sixfold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately tenfold lower apparent oral clearance compared with extensive metabolizers [30,32]. Because of minimal accumulation with once-daily dosing, no dosage adjustment is needed for pediatric CYP2C19 poor metabolizers as in adults [30,33].

Intravenous PK studies in pediatrics

Although intravenous pantoprazole has been used in the pediatric intensive care units (ICU), only a few studies have been reported on the disposition of intravenous pantoprazole in this setting [32,34,35]. Of these, one is an abstract only [34]. The PK of intravenous pantoprazole in 20 pediatric ICU patients was characterized

to determine the influence of demographic factors, systemic inflammatory response syndrome (SIRS), hepatic dysfunction and concomitantly used CYP2C19 inducers and inhibitors [35]. Patients' age range was 10 days to 16.4 years and were considered to be at risk for or had upper gastrointestinal bleeding. They received pantoprazole doses ranging from 19.9 to 140.6 mg/1.73 m^2/day. A total of 156 samples were obtained to study PK using a population PK approach. Pantoprazole PK was best described using a two-compartment model with zero order infusion and first-order elimination. Interindividual variability in 75% of patients was due to body weight, SIRS, age, hepatic dysfunction and presence of CYP2C19 inhibitors. Central volume of distribution (Vc) was dependent on body weight. The CL and V_c were estimated to be 5.28 l h (-1) and 2.22 l, respectively in the final population model for a 5-year-old child weighing 20 kg. Pantoprazole CL increased with weight and age, and coexistence of SIRS, CYP2C19 inhibitors and hepatic dysfunction significantly decreased pantoprazole CL by 62.3, 65.8 and 50.5%, respectively; if these situations were present separately. In absence of these factors; the predicted pantoprazole CL was faster than that reported in adults. These observations may guide physicians in selecting a starting dose and dosing frequency of pantoprazole for ICU patients with or without such comorbidities.

In the abstract of the intravenous pantoprazole PK study, 14 pediatric ICU patients were randomly administered 0.8 or 1.6 mg/kg of intravenous pantoprazole over 15 min [34]. Pantoprazole PK in patients aged 2–16 years was reported to be similar to that in adults; its CL and Vd increased with weight gain.

Kearns *et al.* also described PK disposition of intravenous pantoprazole in 2–16 year old hospitalized and nonhospitalized patients by giving a single intravenous dose of either 0.8 mg/kg or 1.6 mg/kg of pantoprazole using noncompartmental methods analysis to determine the plasma concentration–time data for each patient. These results are described in the oral PK section, as both studies were performed together [31].

Intravenous pantoprazole was well tolerated in these studies in pediatric patients. The results suggest that using intravenous pantoprazole dosing may provide similar drug exposure as adults. There are several limitations that limit general application of these observations. The potential for drug interactions in patients receiving concomitant medications that may have influenced the PKs of intravenous pantoprazole have not been addressed in all studies. The limited number of patients on each concomitant medication prevents evaluation of drug–drug interactions with the modeling approach used in these studies. Although the PK data obtained from these patients may indicate drug–drug interactions; data may fall within the normal range of variability in pantoprazole PKs due to the limited number of patients. In addition, the effect of the severe concomitant medical conditions in these hospitalized patients was evaluated in only one study [35]. Furthermore, PD effects of intravenous pantoprazole were not assessed, so the efficacy and therapeutic potential of the doses studied remain unknown at this time.

In pediatric patients aged 1 through to 16 years, there were no clinically relevant effects of gender on clearance of pantoprazole, as shown by population PK analysis. No dosage adjustment is necessary in patients with renal impairment, in patients undergoing hemodialysis, or in patients with mild-to-severe hepatic impairment [101].

Dosage forms

Pantoprazole is available in two doses as tablets, in one dose formulation as granules and in intravenous dose formulation in the USA [101]. Delayed-release tablets: 40 and 20 mg tablets to be taken 30 min before a meal.

Delayed-Release oral suspension: 40 mg, pale yellow-to-dark brownish, enteric-coated granules in a unit dose packet. Pantoprazole oral suspension should be taken 30 min before a meal. It should only be taken with applesauce or apple juice 30 min before a meal. Pantoprazole should not be taken with water or other liquids, or with other foods. Pantoprazole oral suspension should not be chewed or crushed. In the suspension form, administration by nasogastric or gastrostomy tube is feasible.

Intravenous formulation: 40 mg/vial.

Adverse reactions

All adverse reactions to pantoprazole observed in adults are possible in pediatric patients. In patients aged 1–16 years, upper respiratory infection, vomiting, headache, rash, fever, stomach pain and diarrhea contributed to >4% of adverse reactions.

Other less common adverse reactions reported in <4% of pediatric patients enrolled in clinical studies are: allergic reaction, facial edema, constipation, flatulence, nausea, elevated triglycerides, elevated liver enzymes, elevated CK (creatine kinase), arthralgia, myalgia, dizziness, vertigo and urticaria.

Although not observed in pediatric trials, photosensitivity reaction, dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leucopenia and blurred vision have been reported in adults, so prescribing physicians should be aware of them.

Drug interactions

Concomitant use of atazanavir, nelfinavir or coumarin anticoagulants with PPIs is not recommended. Furthermore, pantoprazole may interfere with absorption and bioavailability of drugs such as ketoconazole, ampicillin esters and iron salts [101].

Other potential uses of PPIs

Although not approved, pantoprazole could theoretically be used in the management of gastrointestinal bleeding, *Helicobacter pylori* infection and other conditions where acid suppression is considered beneficial [36,37].

Long-term use of pantoprazole in pediatric age

Gastroesophageal reflux in infants and very young children is usually benign and are usually resolved by the age of 18 months [3]. Most pediatric patients with GERD do well with a course of medications such as PPIs, although a relapse after cessation of medical therapy can happen [38]. Step-down treatment from PPIs to H_2RAs and eventual weaning is not always smoothly accomplished and it may even be impossible to discontinue it in some patients. This may indicate the need for long-term maintenance therapy. Long-term use is often empiric without appropriate indications. PPIs are not benign medications and longer than approved use should be closely monitored. Furthermore, diagnosis of GERD should be objectively documented if prolonged use is to be considered. Although PPIs have a few adverse effects, they are usually well tolerated for long-term use. Recent epidemiologic studies suggest some possible risks including interference with calcium homeostasis and aggravation of cardiac conduction defects. These agents have also been responsible for hip fracture in postmenopausal women. Potential inhibition of gastric secretion of acid, pepsin and intrinsic factors as well as absorption of vitamin C, iron and other substances has given rise to concerns about a number of possibly resulting clinical deficiency states. Other areas of concern are: hypomagnesemia; increased incidence of pneumonia, enteric infections and hypergastrinemia. Recently, cancer, small bowel bacterial overgrowth and drug interactions have also been reported [39,40]. The benefits of prolonged PPI use must be balanced against potential risks in all patients.

Tolia *et al.* reported long term continuous use of several PPIs in 113 children and adolescents for longer than a year in a retrospective study [41]. Omeprazole, lansoprazole, pantoprazole and esomeprazole were prescribed in this cohort. A total of eight age range 6.1–15.9 years (mean 11.5) were treated with pantoprazole for 9–64 months (mean duration 32 [21.4] months). There were equal number of males and females and the dose ranged from 0.58–1.41 mg/kg/day. It was administered once daily in three and twice daily in five patients. The indications were abdominal pain, choking, dysphagia, heartburn and chest pain. As many of seven patients had no adverse effects, one had vomiting and diarrhea. As expected, hypergastrinemia occurred in five patients. A review and systematic analysis for maintenance PPI treatment in the pediatric age group for the management of GERD has been recently published [42]. It suggests that such a need is highest in GERD patients with other comorbidities. PPIs were effective and safe for maintenance treatment of GERD symptoms and reflux esophagitis.

Although PPIs as a class of drugs have a track record of safety, with increased use, side effects of considerable clinical importance, albeit in low incidence, are being gradually noticed, especially in long-term users. Although such side effects may be relevant only to a minority of cases, healthcare providers need to be aware of their occurrence and ways to monitor for better management of their patients. Future prospective and, when possible, randomized, studies designed to measure safety, with minimal confounding are needed to assess the real importance of such events associated with their use in all ages.

Future perspective

While the doses used in these studies were well tolerated; There is still a need for additional clinical trials with pantoprazole in the treatment of children with more severe GERD. Limitations of current data include the small size of the study population and the exclusion of patients who are <5 or >95 percentile for weight. Studies of parallel groups with other active comparators such as H_2RAs or alternative PPIs would be desirable to obtain additional efficacy data. Healing of erosive esophagitis after treatment with oral pantoprazole has been shown in pediatric studies,

PD effects and healing of reflux esophagitis with pantoprazole have not been assessed extensively. Although it may be a viable treatment option for GERD in hospitalized pediatric patients in whom oral therapy is not feasible, further PD and clinical studies are needed to determine if intravenous pantoprazole may be an acceptable alternative to oral route for the efficacious treatment of GERD in pediatric patients for whom oral therapy is not possible.

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Executive summary

- Pantoprazole has been reported to be effective in relieving gastroesophageal reflux disease (GERD) symptoms in children and adolescents. Among pediatric patients with GERD (suspected clinically or proven by investigations) in interventional trials with pantoprazole, most experienced improvement in persistent, troublesome GERD symptoms with pantoprazole therapy. A few had partial amelioration of symptoms.
- New clinical, pharmacodynamic, pharmacokinetic and limited pharmacogenomic data on pantoprazole have been published in the last few years and it has been studied in premature babies, neonates, infants, children and adolescents.
- There was no improvement in symptoms in infants under a year of age compared with placebo.
- It is well tolerated and its side-effect profile is safe and similar to that in adults.
- Upper respiratory infection, vomiting, headache, rash, fever, stomach pain and diarrhea are most common accounting for >4% of adverse reactions. Adequate monitoring of patients is recommended to avoid other untoward reactions.
- Randomized, placebo-controlled studies are needed to further assess the role of pantoprazole in the management of pediatric GERD.
- Based on these observations, the US FDA has approved pantoprazole for pediatric patients aged 5–16 years with GERD for up to 8 weeks of treatment.
- It is available as 20 and 40 mg tablets, 40 mg sachet for oral use and as 40 mg/ml for intravenous use.

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