Proton Pump Inhibitor Use in Infants: FDA Reviewer Experience

*Ii-Lun Chen, *Wen-Yi Gao, *Aisha P. Johnson, *Ali Niak, *John Troiani, *Joyce Korvick, *Nancy Snow, ‡Kristina Estes, †Amy Taylor, and *Donna Griebel

ABSTRACT

The Food and Drug Administration has completed its review of 4 clinical trials evaluating the use of proton pump inhibitors (PPIs) in infants (ages 1 month to <12 months) for the treatment of gastroesophageal reflux disease (GERD). An Advisory Committee meeting was held in November 2010 to discuss the potential reasons why PPI use in these trials failed to show a benefit in infants with GERD, and directions for future study. The present review summarizes the findings from the clinical trials. Potential mechanisms for the failed clinical trials are discussed. The safety of long-term use is also discussed. As a result of our analysis and review, the authors agree with the Advisory Committee members that PPIs should not be administered to treat the symptoms of GERD in the otherwise healthy infant without the evidence of acid-induced disease.

Key Words: Advisory Committee, clinical trials, efficacy, GERD, infants, proton pump inhibitor, safety

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The use of proton pump inhibitors (PPIs) in infants has increased over time. Among pediatric patients <12 months old, there was an 11-fold increase in the number of new prescriptions dispensed between 2002 and 2009 (1).

Comprehensive guidelines recently published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition-European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN-ESPGHAN) state that gastroesophageal reflux disease (GERD) is ''present when the reflux of gastric contents causes troublesome symptoms and/or complications (2).'' Because of the unique characteristics of the infant stomach, feeding schedule, and acid production compared with older children and adults, gastric refluxate enters the esophagus much more frequently than in adults (3). In most infants, this does not cause distress, and is designated as gastroesophageal reflux (GER); if it causes distress, it is designated GERD (2). The present review pertains to PPI use in GERD.

The natural history of symptomatically (nonendoscopically) diagnosed GERD in infancy, particularly spitting up, is spontaneous resolution (4). Once a patient presents with signs of GERD (regurgitation, crying, arching back), management in primary care settings usually begins with a trial of conservative measures such as thickened, frequent, and smaller feeds, and frequent burping. If the infant responds favorably, conservative measures are maintained until resolution; however, if the infant does not respond, other etiologies, such as anatomic anomalies and cow milk protein intolerance, are evaluated. In routine clinical practice, if conservative measures and a search for alternative etiologies fail to relieve signs and symptoms, then antacids, H_2 blockers, or PPIs may be initiated. The NASPGHAN guidelines state in infants with ''unexplained crying and/or distressed behavior'' that expert opinion suggests that ''if irritability persists with no explanation other than that of suspected GERD,'' the risk/benefit ratio of a time-limited (2-week) trial of antisecretory therapy ''is not clear'' (2). The guideline cautions that there are potential side effects of the PPIs, and that clinical improvement following empiric therapy may be because of spontaneous symptom resolution.

There are presently no PPIs approved by the Food and Drug Administration (FDA) for use in infants younger than 12 months. Four randomized controlled trials have been completed in infants with a clinical diagnosis of symptomatic GERD. None of the PPI studies (esomeprazole, lansoprazole, pantoprazole, or omeprazole) demonstrated efficacy in infants with GERD. The present review summarizes the efficacy results of these trials, and available pharmacokinetic (PK), pharmacodynamic (PD), and safety data in infants. Given the absence of benefit attributable to PPI use in otherwise healthy infants without a documented acid-induced condition, their use in GERD cannot be recommended.

PATIENTS AND METHODS

Data Sources

The following publically available data sources for these 4 PPIs (esomeprazole (5), lansoprazole (6), pantoprazole (5), omeprazole (7)) were used in this analysis:

1. FDA Clinical Reviews of New Drug Applications submitted by drug manufacturers (applications were reviewed involving AstraZeneca's esomeprazole [NEXIUM] and omeprazole [PRILOSEC]; Takeda's lansoprazole [PREVACID]; and Pfizer's pantoprazole [PROTONIX])
2. FDA Advisory Committee (AC) meeting proceedings from November 5, 2010
3. PPI utilization data presented at a June 2010 FDA Pediatric AC meeting to review safety of PPIs in the pediatric age group.

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From the *Division of Gastroenterology and Inborn Errors Products, the †Pediatric and Maternal Health Staff, Office of New Drugs, and the ‡Division of Clinical Pharmacology III, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

Address correspondence and reprint requests to Wen-Yi Gao, MD, PhD, Division of Gastroenterology and Inborn Errors Products, Bldg 22, 10903 New Hampshire Ave, Silver Spring, MD 20993-0002 (e-mail: wen-yi.gao@fda.hhs.gov).

Drs Ii-Lun Chen and Wen-Yi Gao participated equally in the preparation of this manuscript and share first authorship.

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Clinical Trial Selection

To date, 4 randomized controlled trials have been completed evaluating use of PPIs to treat clinically diagnosed GERD in infants ages 1 month to <12 months. These trials were conducted by pharmaceutical companies in response to requests by the FDA. Pediatric Written Requests were issued for trials of omeprazole, lansoprazole, pantoprazole, and esomeprazole under the authority of the Food and Drug Modernization Act (8). Postmarketing requirements to conduct trials were initially issued for lansoprazole, pantoprazole, and esomeprazole under the Pediatric Rule, and later upheld under authority given by the Pediatric Research Equity Act (9).

Data Extraction

Data were extracted directly from the publically available FDA Clinical Reviews.

Study Populations

The study population characteristics in these trials are shown in Table 1. All of the trials, except that for omeprazole, exclusively enrolled patients between 1 and 12 months of age (5,6). For omeprazole, the 1 to <12 months age group made up 90% of the study population (7). All of the studies enrolled fewer than 100 patients per study arm and permitted enrollment of infants with a diagnosis of GERD based on clinical presentation. Enrolled infants were to be otherwise healthy, meaning that infants who had clinically significant medical conditions (eg, gastrointestinal anatomic disorders, serious infections, unstable organ diseases, use of certain concomitant medications) were excluded. Endoscopy and other procedures (eg, pH-metry) were not required, and only a few patients in these studies had previous endoscopy.

Study Designs

The designs of these trials are summarized in Table 2.

Study Primary Endpoints

The primary efficacy endpoints used in these trials are listed in Table 3.

RESULTS

Primary Efficacy

The primary efficacy results of the 4 PPI trials are shown in Table 4. In the clinical trials of esomeprazole, lansoprazole, and pantoprazole, which were double-blinded and placebo-controlled trials, there were no statistically significant between-group differences. In the case of the omeprazole trial, which was single-blinded and lacked a placebo control group, between-group comparisons to the lowest (0.5 mg/kg) dose group were not statistically significant (5,6). For omeprazole, mean daily vomiting/regurgitation episodes decreased by 4.34, 2.97, and 4.35 episodes per day (during the last 72 hours) in the 0.5-, 1.0-, and 1.5-mg/kg dose groups, respectively, and all of the confidence intervals included zero (7). Interpretation of the omeprazole data is limited by the trial's single-blinded, uncontrolled design and its inclusion of some patients (10%) older than 12 months of age (7).

Safety

No deaths occurred in any of the infant PPI trials. The most common adverse events were upper respiratory infection, fever, cough, and diarrhea, conditions seen frequently in this age group. There were no clinically significant findings in laboratory measures, including hematology and chemistry, or in vital signs and physical examination.

In the clinical trials of esomeprazole and lansoprazole, there were no clinically meaningful differences of the common adverse events between the treated groups and placebo groups. For pantoprazole, otitis media, rhinitis, laryngitis, and elevated creatine kinase were more common in the treated group compared with the placebo group (difference of ≥4%). The clinical significance of these differences is not clear. The omeprazole trial had a dose-ranging design. It did not appear that there were more adverse events with dose escalation. The incidences of the adverse events were comparable across the 4 PPIs. Of note, the trials were relatively brief in duration, 4 to 8 weeks, so the ability to make conclusions regarding the safety profile for longer periods of exposure in this population is limited.

Additional Information

PK and PD information were used to select the PPI doses for infants in the randomized controlled trials. These data are summarized below.

Pharmacokinetics

The PK of 3 PPIs, esomeprazole, lansoprazole, and pantoprazole, have been studied in infants ages 1 month to 1 year. A granule formulation of each drug was developed for use in these pediatric studies. Two dose levels were included in each PK study (Table 5). PK parameters for all 3 drugs were greatly variable in this age group.

Esomeprazole The PK of oral esomeprazole was evaluated in 35 infants who received either 0.25 or 1 $mg \cdot kg^{-1} \cdot day^{-1}$ for 7 days (10). Mean esomeprazole exposure in infants who received

TABLE 1. Population characteristics of phase III PPI trials in infants

Population characteristic	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Age, 1–<12 mo	Yes	Yes	Yes	Yes*
Sample size, per arm	40	80	50	35
Clinical diagnosis of GERD	Yes†	Yes†	Yes†	Yes‡

Referenced from Data Sources Section. GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.
* Study population was 0–24 months age group; 90% of patients were younger than 12 months.
† Patients had signs of GERD or endoscopically proven GERD.
‡ Patients had signs of GERD for at least 2 months.

TABLE 2. Study designs of PPI efficacy and safety trials in infants

Study design feature	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Randomized	Yes	Yes	Yes	Yes
Control group	Placebo	Placebo	Placebo	Dose ranging
Blinding	Double	Double	Double	Single
Trial of conservative measures	No	Yes	Yes	Yes
Open-label enrichment phase to identify PPI responders	Yes (2 wk)	No	Yes (4 wk)	No
Randomized withdrawal from PPI	Yes	No	Yes	No
Antacids allowed	Yes (as rescue)	No	Yes (as rescue)	Yes
Length of randomized phase	4 wk	4 wk	4 wk	8 wk

Referenced from Data Sources Section. PPI = proton pump inhibitor.

$1\,mg \cdot kg^{-1} \cdot day^{-1}$ was similar to that in children 1 to 11 years who received 10 mg/day, adolescents who received 20 mg/day, and adults who received 20 mg/day. Infants who received $0.25\,mg \cdot kg^{-1} \cdot day^{-1}$ had exposures that were 76% to 82% lower than exposures observed in other age groups who received 10 to 20 mg/day.

Lansoprazole The PK of oral lansoprazole was evaluated in 24 infants who received 1 or $2\,mg \cdot kg^{-1} \cdot day^{-1}$ for 5 days (11). Mean lansoprazole exposure in infants who received $1\,mg \cdot kg^{-1} \cdot day^{-1}$ was similar to children 1 to 11 years old who received a weight-based regimen of either 15 or 30 mg/day for children $\leq$30 or >30 kg, respectively. The exposure in these infants was similar to adolescents (12–17 years) and adults who receive 30 mg/day. Mean lansoprazole exposure in infants who received $2\,mg \cdot kg^{-1} \cdot day^{-1}$ was approximately 2- to 3-fold higher than exposures observed in adolescents and adults who receive 30 mg/day.

Pantoprazole The single-dose PK of oral pantoprazole was evaluated in 21 infants who received an average dose of 0.6 mg/kg and in 20 infants who received an average dose of 1.2 mg/kg (12). Dosing in this trial was not based on weight; instead, a single-dose level was assigned to a particular weight band, as described in Table 5. Mean pantoprazole exposure in infants who received the average dose of 1.2 mg/kg was 20% to 35% lower than adults who received a single dose of 40 mg but similar to children (6–11 years) and adolescents (12–17 years) who received 40 mg/day. Mean pantoprazole exposure in infants who received the average dose of 0.6 mg/kg was 70% to 78% lower than children (6–11 years), adolescents (12–17 years), and adults who received a single 40-mg dose.

Pharmacodynamics

Two dose levels were included in each infant PD study (10–12). Intragastric pH and percentage time pH exceeded 4 were evaluated. The utility of these PD endpoints in the management of infant symptomatic GERD has not been established. No consistent dose-response relation was observed for the 3 PPIs for which data are available. The data from these studies are summarized in Table 6.

The PD effect, as measured by the percent time pH > 4 during the 24-hour dosing interval, is greater than or equal to the response observed in adults. This trend suggests that appropriate

TABLE 3. Primary endpoints of phase III PPI trials in infants

Proton pump inhibitor	Primary endpoint	Assessment tool for primary endpoint
Esomeprazole (NEXIUM)	Time from randomization to discontinuation because of symptom worsening*	PGA† of patient's GERD signs
Lansoprazole (PREVACID)	Responder‡ rate in randomized double-blind treatment period	Daily diary of patient's GERD signs by parent/caregiver, PGA, and physical examination
Pantoprazole (PROTONIX)	Proportion of patients who withdrew because of lack of efficacy§	Patient diary rating of various signs associated with GERD
Omeprazole (PRILOSEC)	Change from baseline in daily mean vomiting/regurgitation episode frequency during last 72 h	Patient diary card and PGA

Referenced from Data Sources Section. GERD = gastroesophageal reflux disease; PGA = Physician's Global Assessment.

* Symptom class included vomiting/regurgitation, irritability, supraesophageal and respiratory disturbances, and feeding difficulties; Parent and Physician Symptom Severity Assessment Scale included none (0), mild (1), moderate (2), and severe (3); symptom worsening defined as worsening by 1 ordinal category based on physician assessment of parental reports.

† Physician's Global Assessment: Overall clinical impression of the patient's GERD-related symptoms during the last 7 days as none (no symptoms), mild (symptoms present but not interfering with daily activities), moderate (symptoms present and somewhat interfering with daily activities), or severe (symptoms present and greatly interfering or preventing daily activities).

‡ Patient was defined as a "responder" if he/she had ≥50% reduction from baseline in number of feeds with crying/fussiness/irritability or in average duration of such episodes.

§ "Lack of efficacy": significant worsening of GERD symptoms, and/or maximal antacid use for 7 consecutive days, and/or worsening esophagitis on endoscopy, and/or physician judgment.

TABLE 4. Primary efficacy results of phase III PPI trials in infants

PPI medication	Primary efficacy result relative to control
Esomeprazole	Hazard ratio 0.69 (PPI/placebo) 95% CI 0.35–1.35 ($P = 0.275$)
Lansoprazole	Responder rate (PPI vs placebo) 54.3% (44/81) vs 54.3% (44/81) ($P = 1.000$)
Pantoprazole	Responder rate (PPI vs placebo) 12% (6/52) vs 11% (6/54) ($P = 1.000$)
Omeprazole	Adjusted LS means (ANCOVA)*: 0.5 mg/kg dose −4.34 (−8.5 to −0.15) 1.0 mg/kg dose −2.97 (−7.0 to 1.06) 1.5 mg/kg dose −4.35 (−8.2 to −0.46) (All pairwise comparisons to 0.5 mg/kg dose had $P > 0.50$)

Referenced from Data Sources Section. ANCOVA = analysis of covariance; CI = confidence interval; LS = least square; PPI = proton pump inhibitor.
* Adjusted least square means (ANCOVA): 3 patients from intent-to-treat population were excluded as extreme outliers.

doses were selected for study in the infant trials. Although there is a clear dose-response relation for esomeprazole from 0.25 to $1\,mg \cdot kg^{-1} \cdot day^{-1}$, the dose-response relation for lansoprazole and pantoprazole is less apparent. For lansoprazole, this may be because of a selection of doses that were at or above the maximum effective dose. In addition, PD data were available from only 3 patients in each lansoprazole dose group.

FDA's Gastrointestinal Drugs Advisory Committee Meeting, November 5, 2010

On November 5, 2010, a Gastrointestinal Drugs AC meeting was held to discuss the results from the 4 randomized controlled trials of PPIs in pediatric patients with symptomatic GERD, who were younger than 12 months. AC members were screened for potential conflicts of interest in accordance with applicable laws, regulations, and policies. To interpret the consistently negative results from these trials, the committee re-evaluated the pathophysiology, diagnosis, and management of GERD, and issues related to the trials' designs. A brief summary of the proceedings follows.

In adults, symptomatic GERD is known to be secondary to acid reflux, as is erosive esophagitis in infants. In contrast, for most infants with classic signs and symptoms of GERD, acid reflux has never been demonstrated to be causative, but transient relaxation of the lower esophageal sphincter probably plays a role. The AC suggested that for future pediatric studies of acid-suppressing agents for symptomatic GERD, pediatric trials in infants should be limited to acid-induced conditions (eg, erosive esophagitis). For example, certain pediatric populations have underlying conditions that predispose them to acid-induced pathology (eg, neurological diseases, congenital esophageal lesions, tracheal esophageal fistula).

The AC generally agreed that for new products intended to treat pediatric conditions in which acidity is a key contributor, pediatric clinical trials are needed to obtain PD and PK and long-term safety data. In these cases, efficacy can be extrapolated from adult data. The effect of CYP450 enzyme ontogeny on PPI PKs should be investigated in relation to dosing in the various pediatric age groups (age groups may be categorized as neonates [0–<1 month], infants [1 month–<1 year], children [1–11 years], and adolescents [12–17 years]).

Most AC members concurred that use of endoscopy and instruments, measuring patient-reported outcomes (eg, the Infant Gastroesophageal Reflux Questionnaire) in clinical trials of infants with symptomatic GERD, should be explored further. Data on posttreatment repeat endoscopies and more guidance on performing biopsies in this patient population are needed. Traditional pH-probe monitoring, although useful in measuring the PD effect of PPIs, is not useful as a primary clinical outcome measure because pH and GERD symptoms are poorly correlated. Multichannel intraluminal impedance monitoring may be considered for use in future studies because it provides improved time-event relation and detection of both acid and nonacid reflux compared with traditional pH probes. Improved detection of reflux associated with retrograde bolus movement and differentiation between acid and nonacid reflux may allow us to select appropriate patient populations when evaluating PPIs for GERD. In addition, biomarkers of tissue injury should be explored.

DISCUSSION

Despite a lack of evidence to support their effectiveness in infant symptomatic GERD, PPI use in infants has increased over time. Among pediatric patients younger than 12 months, nearly 404,000 prescriptions were dispensed to 145,000 patients nationwide in 2009 (1,13). This represents an 11-fold increase in prescriptions from 2002. Interestingly, the proportion of new patient prescriptions for any PPI decreased in this age group during the years 2002 to 2009. This indicates that although new prescription use was decreasing, chronic use was likely increasing, resulting in

TABLE 5. Mean PK parameters following oral administration of PPIs in infants

PPI medication	Dose	C_{max}, ng/mL*	AUC, ng · h/mL†
Esomeprazole	0.25 mg/kg	135 (123) n = 17	463 (113) n = 9
	1 mg/kg	494 (150) n = 17	1834 (103) n = 7
Lansoprazole	1 mg/kg	959 (49) n = 12	2203 (104) n = 12
	2 mg/kg	2087 (75) n = 12	5794 (97) n = 12
Pantoprazole	2.5 mg (2.5–<7 kg); 5 mg (7–15 kg)	503 (100) n = 21	1137 (99) n = 13
	5 mg (2.5–<7 kg); 10 mg (7–15 kg)	1384 (94) n = 20	3709 (90) n = 18

Percent coefficient of variation, data from references in corresponding text. PK = pharmacokinetic; PPI = proton pump inhibitor.
* C_{max}, peak plasma concentration.
† AUC, area under the plasma concentration time curve.

TABLE 6. Mean PD parameters of 3 PPIs in infants

PPI medication	Dose, mg/kg	Intragastric pH*		Percent time intragastric pH > 4	
		Baseline	Steady state	Baseline	Steady state
Esomeprazole	0.25	2.3 (n = 25)	3.6 (n = 22)	30.5 (n = 25)	47.9 (n = 22)
	1	2.2 (n = 23)	5.6 (n = 22)	28.6 (n = 23)	69.3 (n = 22)
Lansoprazole	1	NA	NA	50 (n = 3)	84.9 (n = 3)
	2	NA	NA	52.4 (n = 3)	83.9 (n = 3)
Pantoprazole	0.6	4.2 (n = 11)	4.8 (n = 11)	55.5 (n = 11)	68.5 (n = 11)
	1.2	3.1 (n = 10)	4.2 (n = 10)	32.2 (n = 10)	56.6 (n = 10)

Referenced from corresponding text. NA = not available; PD = pharmacodynamic; PPI = proton pump inhibitor.
* Median values for esomeprazole, mean values for pantoprazole.

an overall increase in PPI prescriptions. General practice/family medicine and internal medicine were the top prescribing specialties of PPIs for all of the pediatric age groups in 2009. ''Esophageal Disorder Not Elsewhere Classified'' (*ICD-9 530.8*) was the top diagnosis code recorded for all of the age groups for the review period (14). Among the US commercially insured population, the median age of initiation of PPIs in pediatric patients younger than 2 years was 226 days. The median duration of use for children 12 years of age and younger was 60 days (15). In a retrospective observational study using data from 1999 to 2004 from 4 health care plans in the United States involving 2469 infants younger than 12 months, Barron et al (16) report a mean age of first PPI use of 4 to 5 months, with treatment discontinued in most patients by 7 to 8 months of age.

Several key issues should be considered when using PPIs in infants: whether an individual infant's GERD presentation is acid related, gastrin effects, strength of evidence that PPIs are effective for treatment of GERD in this population, and long-term safety.

Gastric Acid Secretion and PPI Use in Infants

The use of PPIs to treat GERD in infants is based on the assumption that acid reflux is the cause of their GERD symptoms. What is known about the relative contribution of gastric acid to GERD in the adult versus pediatric population is an important issue to consider. Although a study by Boyle et al (17) found that acid secretion rates adjusted by body weight (milliequivalent per kilogram per hour) in adults were similar to acid secretion rates for infants younger than 1 year, other studies that did not adjust for body weight (milliequivalent per hour) found that acid secretion rates of adults are significantly higher than infants, with the rate varying from study to study (18–21). For example, the maximal acid secretion rate on the first day of life is approximately 0.03 mEq/hour, which is about 430-fold lower than adults (13.06 mEq/hour) (18–23). By the end of 4 months, the average secretion rate of infants is about 27-fold lower than adults (0.47 vs 13.06 mEq/hour) (19). It is unclear whether body weight–adjusted esophageal acid exposure provides the most relevant means of comparing infants to adults. Other important factors affecting acid exposure of the esophageal epithelium in infants include lower esophageal sphincter tone and feeding frequency, neither of which requires body weight adjustment. Reflux of non-acidic stomach contents may cause GERD symptoms in infants such as fussiness, arching, regurgitation, or burping (24).

Gastrin and Rebound Hypersecretion

It has been reported that adult patients experience acid rebound after withdrawal of PPI therapy, which can lead to PPI dependency (25). Reports in the pediatric literature have also shown that gastrin levels are elevated in the majority of pediatric patients (infants through adolescents) on prolonged PPI therapy, but elevated gastrin levels return to normal in 23% to 38% of patients after long-term treatment (26).

Among the 4 infant PPI trials, only the pantoprazole trial collected serum gastrin measurements. After 4 weeks of open-label treatment with pantoprazole, mean gastrin levels increased approximately 50% over baseline. At the final assessment after a 4-week randomized treatment period, the mean gastrin level in patients randomized to pantoprazole remained elevated, whereas in those randomized to placebo gastrin levels trended back toward baseline. There was no evidence of symptom rebound during the withdrawal phase, despite elevated gastrin levels at the end of the open-label phase; however, the observed outcomes may have differed if concomitant antacid therapy had been controlled.

Absence of Evidence That PPIs Are Effective for Treatment of GERD in Infants

Although the PK and PD data indicated that appropriate PPI doses had been identified to suppress gastric acid, all of the clinical trials conducted to investigate whether 4 different PPIs were effective for treatment of GERD in infants failed to demonstrate PPI efficacy in this population. The consistency in this observed outcome suggests that the symptoms upon which the clinical diagnosis of GERD was made for infants who entered these trials (eg, fussiness, regurgitation, gagging with feeds) are not manifestations of acid reflux disease. Alternatively, the endpoints used in the trials may not have been adequate; however, the endpoints were based on assessments of classic symptoms that are the foundation for making the clinical diagnosis of GERD in infants. For this reason, the endpoints do seem clinically relevant because they are the symptoms that cause parents to seek care for their infant.

Long-term and Serious Safety Concerns With PPI Use

There are potential risks associated with PPI use (2). Clinical trials of PPIs in infants are of short duration (4–8 weeks). The adverse events observed associated with short-term use cannot be assumed to be the same as those when PPIs are used during long periods of time. Although PPIs generally have been considered safe, there are safety concerns associated with long-term use.

Among adults, there have been concerns that long-term PPI use may predispose patients to an increased risk of gastric cancer, gastric carcinoid tumors, and colorectal cancer. These concerns are

based on hypergastrinemia, alteration of the distribution of gastritis, and accelerated development of atrophic gastritis, in the presence of *Helicobacter pylori* infection (27). Suppression of gastric acid secretion may also predispose patients to certain infections (*Clostridium difficile* infections, other enteric infections, and respiratory infections, including community-acquired pneumonias). The mechanism for this may be that acid suppression eliminates a defense against pathogens (28).

There have been rare reports of vitamin and electrolyte abnormalities (eg, vitamin B_{12} (29) deficiency and hypomagnesemia (30)) in adults taking PPIs chronically. There have been cases of hypomagnesemia that required discontinuation of the PPI in addition to magnesium supplementation (31). Observational studies and postmarket reports (32) of calcium deficiency and osteoporosis in adults on chronic PPI therapy recently led FDA to require class labeling of these adverse effects for all PPIs; however, further studies are needed to discern the exact mechanism for these fractures. It is not known whether calcium malabsorption fully accounts for this observation. Additionally, PPIs have been implicated as a cause of acute interstitial nephritis (29).

Within the context of the small trials of relatively short duration described in this review, PPIs appeared relatively safe in infants younger than 1 year. In the literature, there have been reports of adverse events related to the use of chronic PPIs in infants; for example, acid suppression has been linked to higher rates of necrotizing enterocolitis in extremely low-birth weight infants (33). We do not yet fully understand the consequences of reduced gastric acid on the intestinal microflora of infants. The safety concerns associated with PPI use in adults, including negative effects on bone integrity, are important to consider for children. An appropriate assessment of the risk/benefit of PPI use in infants requires an understanding of their therapeutic benefit in this population.

SUMMARY

The FDA reviewed 4 randomized controlled trials evaluating the use of PPIs in infants (ages 1 month to <12 months) for the treatment of symptomatic GERD. An AC meeting was held in November 2010 to discuss the pathophysiology and diagnosis of infant GERD and possible reasons why the trials failed to show effectiveness, despite the use of a range of endpoints to assess efficacy. Based on FDA's independent review and the expert advice of the AC members, the authors offer the following conclusions:

1. Clinical efficacy was not demonstrated in the controlled clinical trials evaluated, even though the pharmacodynamic studies predicted that the PPI doses evaluated in these trials would have raised the gastric pH. In the absence of demonstrated efficacy of PPIs for the treatment of GERD in infants, the authors agree with the AC members that health care practitioners should not prescribe PPIs for the otherwise healthy infant, 1 month to <12 months old, as initial treatment for symptomatic GERD. Rather, infants with symptoms of GERD should be initially treated with conservative measures (eg, infant positioning and changes in diet) and evaluated for milk protein allergy. The majority of these infants improve over time with conservative measures and do not have acid induced disease that will benefit from PPI administration. If conservative measures and a search for alternative etiologies fail to relieve signs and symptoms, then consultation with a pediatric gastroenterologist may be warranted for further evaluation and management.
2. Use of PPIs should be reserved for infants with an endoscopically documented acid-induced condition such as erosive esophagitis. The risk/benefit relation of administration of PPIs in infants with GER or GERD without a documented acid-induced condition is not favorable because no benefit can be attributed to the PPI. Furthermore, there may be risks associated with long-term PPI use that require further study in this young population.
3. Data from short-term PPI trials in infants have not revealed a serious safety signal; however, both short-term and long-term safety data are limited.
4. Presently available diagnostic tools such as symptom scores, survey instruments, and pH-metry are not sufficient to identify the subpopulation of infants with GER that have acid-induced disease that could benefit from PPI use. Multichannel impedance monitoring may be considered in trials of acid-suppressing agents. Endoscopy may be the most reliable method to identify acid-induced esophageal injury.
5. Clinical trials evaluating PPIs may be warranted in subpopulations of infants such as those with erosive esophagitis, cystic fibrosis, and short bowel syndrome (34). In infants with erosive esophagitis, PPI efficacy can be extrapolated from adults; however, trials are needed to determine the appropriate infant dose and evaluate safety. PPIs are frequently used in patients with extraesophageal manifestations of GERD, repairs of anomalies involving the upper and lower gastrointestinal tract, and prematurity (34). These populations also should be considered for enrollment in clinical trials to evaluate PPIs.

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