



## Proton Pump Inhibitor Use in Infants and Children: A Review of the Recent Literature

Marcia L. Buck, PharmD, FCCP, FPPAG, BCPPS

Proton pump inhibitors (PPIs), including omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole, are effective agents for suppressing gastric acid production, making them a useful tool in the treatment of gastroesophageal reflux disease (GERD), erosive esophagitis, or gastric bleeding in children and adults.<sup>1</sup> These drugs account for 95% of prescriptions for gastric acid suppressive agents written in the United States, with more than 150 million prescriptions written for a PPI in 2014. Over-the-counter purchases of PPIs account for more than 10 billion dollars in annual sales world-wide.

Premarketing clinical trials of PPIs documented a mild adverse effect profile; however, the duration of these studies was often 12 weeks or less. After approval by the Food and Drug Administration (FDA), widespread use, often for extended periods, revealed more serious adverse effects. Based on the accumulation of these reports, the FDA issued a safety alert on PPI-associated hypomagnesemia on March 2, 2011, another on the association between extended use of PPIs and fractures on March 23, 2011, and a third describing an increased risk for *Clostridium difficile* infections in patients taking PPIs on February 8, 2012.<sup>2-4</sup> Subsequent studies and meta-analyses have documented an association between PPIs and other enteric infections, hospital or community-acquired pneumonia (CAP), urinary tract infections, decreased absorption of calcium and vitamin B<sub>12</sub>, allergic disease, gynecomastia, obesity, and chronic kidney disease.<sup>1,5</sup> Causal relationships between PPIs and these additional adverse effects have not been fully established.

### Infections

As the result of their inhibition of gastric acid, PPIs alter oropharyngeal and gastric bacterial colonization and the gastrointestinal microbiome, increasing the risk for enteric infections with *C. difficile*, *Salmonella*, and *Campylobacter jejuni*. Use of PPIs has also been associated with an increase in pulmonary translocation of pathogenic

bacteria such as *Streptococcus pneumoniae*, resulting in increased risk for upper and lower respiratory tract infections. In addition, PPIs may impair leukocyte function, further worsening the risk for infection.<sup>1,5</sup>

In 2006, Canani and colleagues, writing as the Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition, compared rates of gastroenteritis and CAP in young children receiving treatment for GERD with healthy controls.<sup>6</sup> The analysis included 186 children between 4 and 36 months of age; 91 receiving gastric acid suppression with either histamine receptor antagonists (H<sub>2</sub>RA) or PPIs and 95 healthy controls. Forty-seven patients in the treatment arm received ranitidine 10 mg/kg/day, and 44 received omeprazole 1 mg/kg/day for 2 months. Results were assessed at 4 months.

Patients receiving gastric acid suppression experienced significantly more episodes of acute gastroenteritis during the follow-up than the controls (47% versus 20%,  $p < 0.001$ ) and higher rates of CAP (12% versus 2%,  $p = 0.02$ ). Logistic regression analysis confirmed the relationship between acid suppression with acute gastroenteritis (OR 3.58, 95% CI 1.87-6.86) and CAP (OR 6.39, 95% CI 1.38-20.70). Comparing baseline and follow-up data in the treated patients also revealed significant increases in gastroenteritis (47% versus 20%,  $p < 0.001$ ) and CAP (12% versus 3%,  $p = 0.02$ ), while there were no significant differences in the control group.

The relationship between PPIs and pulmonary infections has subsequently been studied by a number of investigators, often with a focus on children with underlying immunodeficiency or chronic illness. In 2018, van Horck and colleagues performed the first longitudinal study of the relationship between PPI use and lung function in patients with cystic fibrosis (CF).<sup>7</sup> The authors utilized the Dutch Cystic Fibrosis Foundation database to gather information from 545 children collected between 2009 and 2014.

Decline in lung function was evaluated by change in forced expiratory volume in 1 second as a percentage of the predicted value (FEV<sub>1</sub> % predicted) and the change in rate of pulmonary exacerbations. The potential risk factors assessed included age, gender, body mass index, baseline lung function, genotype, pancreatic insufficiency, CF-related diabetes, allergic bronchopulmonary aspergillosis, colonization with *Pseudomonas aeruginosa*, and the use of PPIs, antibiotics, or inhaled corticosteroids.

The most striking impact on lung disease progression was seen with PPI use. There was a significant annual decline in FEV<sub>1</sub> % predicted, with an estimated pooled effect of -0.69 (95% CI -1.26 to -0.12) after adjustment for other risk factors (p = 0.017). Use of PPIs was also associated with an increase in the rate of pulmonary exacerbations (OR 1.565, 95% CI 1.138-2.151, p = 0.006). Further examination of the data revealed a positive association between length of PPI use and both decline in FEV<sub>1</sub> % predicted (p = 0.020) and exacerbation rate (p = 0.034).

A positive correlation between gastric acid suppression in infants and late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) was demonstrated in a study by Manzoni and colleagues, writing for the Italian Task Force for the Study and Prevention of Neonatal Fungal Infections and the Italian Society of Neonatology.<sup>8</sup> The authors performed a secondary analysis of data from a multicenter randomized controlled trial evaluating the utility of lactoferrin supplementation, with or without *Lactobacillus rhamnosus* GG, for preventing LOS and NEC. Of the 743 infants enrolled, 235 received cimetidine, ranitidine, or omeprazole for GERD, feeding intolerance, or prevention of gastric bleeding during treatment with non-steroidal anti-inflammatory agents to close a patent ductus arteriosus.

Use of gastric acid suppression was significantly and independently associated with the development of LOS (OR 1.03, 95% CI 1.008-1.067, p = 0.01). Each additional day of gastric acid suppression increased the odds of developing LOS by 3.7%. The risk was greatest for development of Gram-negative infections (p < 0.001) and *Candida* spp. fungal infections (p = 0.001). Administration of lactoferrin appeared to lower the additional risk for LOS per day from 7.7% to 1.2%. Findings for NEC were similar, with a significant correlation between gastric acid suppression and the development of NEC (OR 1.023, 95% CI 0.966-1.083, p = 0.044). For each additional day of gastric acid suppression, the risk for NEC increased by 11.4% in the group not

receiving lactoferrin, while the group given lactoferrin showed no increased risk.

Bîrluțiu and colleagues recently described a case of meningoencephalitis in a 9-month-old infant receiving esomeprazole.<sup>9</sup> The patient was admitted after presenting to the emergency department with fever, lethargy, emesis, and a bulging fontanelle. He was previously healthy, except for GERD diagnosed at 2 months of age. He had been receiving esomeprazole 0.5 mg/kg/day for 4 months, which had improved his symptoms. He was found to have leukopenia, with a white blood cell count of 2.6 x 10<sup>9</sup>/L with 88.2% neutrophils. Both C-reactive protein and procalcitonin were significantly elevated. A sample of the patient's cerebrospinal fluid produced a positive latex agglutination test for group B *Streptococcus*, with confirmation on Gram stain of *S. agalactiae*. Antibiotics cleared the infection, but the patient experienced a prolonged recovery with right hemiplegia, language deficits, and episodic irritability. The mother's vaginal tract, breastmilk, and skin were evaluated as a potential source of the infection with negative results. The authors concluded that long-term use of a PPI produced an alteration of the gut microbiome and may have contributed to the patient's leukopenia, setting the stage for this serious infection in an otherwise healthy infant.

### Fractures

The association between PPIs and hip, wrist, or spine fractures has been established in nearly a dozen studies.<sup>10</sup> The increased fracture risk appears to be the result of the effects of both increased gastrin production and gastric acid suppression. Hypergastrinemia caused by PPI exposure produces significant elevations in histamine secretion from enterochromaffin-like cells (ECLCs). Higher circulating levels of histamine have been suggested as a mechanism for increased differentiation of osteoclast precursors. Hypergastrinemia may also spur the development of hyperparathyroidism, resulting in increased levels of osteocalcin and alkaline phosphatase, markers of increased bone turnover. Reduction in gastric acid production also results in clinically significant reductions in the absorption of several micronutrients, including vitamin B<sub>12</sub>, magnesium, and calcium. While not consistent among the studies, the most commonly reported risk factors for fractures include patient age (elderly patients are known to be at higher risk), extended use (1 year or longer), or use of high-dose therapy.<sup>1,3,10</sup> Comorbidities such as osteoporosis or chronic kidney disease, further compound the risk.

A study published by Malchodi and colleagues in the June 2019 issue of *Pediatrics* is the first to have identified an association between PPI use and fractures in children.<sup>11</sup> The authors conducted

a retrospective cohort study of 851,631 children born between 2001 and 2013 who were followed for at least 2 years. Eleven percent received gastric acid suppression in the first year of life: 7,998 (0.9%) received a PPI, 71,578 (8%) were given an H<sub>2</sub>RA, and 17,710 (2%) received both. Infants given acid suppression therapies had an earlier median age at first fracture (3.9 years versus 4.5 years in the untreated group). The use of a PPI increased fracture hazard by 21% (HR 1.23, 95% CI 1.15-1.32) and the use of an H<sub>2</sub>RA with a PPI increased it by 30% (HR 1.31, 95% CI 1.25-1.37). There was no significant impact of H<sub>2</sub> blocker use alone (HR 1.04, 95% CI 0.99-1.09). Length of treatment with a PPI, with or without an H<sub>2</sub>RA, and earlier age at initiation of treatment were both positively correlated with increased risk for fractures.

#### Allergic Disease

In spite of earlier studies attempting to address the issue, there are still questions about the relationship between early exposure to gastric acid suppression and the development of allergies in young children. In the June 2018 issue of *JAMA Pediatrics*, Mitre and colleagues explored this relationship as part of study also evaluating antibiotic exposure.<sup>12</sup> The authors used data from 792,130 children included in the United States Department of Defense (US DoD) TRICARE database between 2001 and 2013. All patients had been enrolled within 35 days of birth and were followed for a mean of 4.6 years. A total of 60,209 (7.6%) of the patients received an H<sub>2</sub>RA, while 13,687 (1.7%) were treated with a PPI during the first 6 months of life. Adjusted hazard ratios for H<sub>2</sub>RA and PPIs for food allergy were 2.18 (95% CI 2.02-2.33) and 2.59 (95% CI 2.25-3.00), respectively, for medication allergy 1.70 (95% CI 1.60-1.80) and 1.84 (95% CI 1.56-2.17), for anaphylaxis 1.51 (95% CI 1.38-1.66) and 1.45 (95% CI 1.22-1.73), for allergic rhinitis 1.50 (95% CI 1.46-1.54) and 1.44 (95% CI 1.36-1.52), and for asthma 1.25 (95% CI, 1.21-1.29) and 1.41 (95% CI, 1.31-1.52). The results from this analysis suggest associations between both H<sub>2</sub>RA and PPIs and the development of allergic disease.

#### Obesity

In a paper published earlier this year by Stark and colleagues, the authors describe an association between drugs that alter the gut microbiome during early childhood and the development of childhood obesity.<sup>13</sup> These authors also used the US DoD TRICARE database to review data from patients born over a period from 2006 to 2013 who received an antibiotic, an H<sub>2</sub>RA, or a PPI in the first two years of life. A total of 333,353 children met the criteria, with 241,502 (72.4%) in the antibiotic group, 39,488 (11.8%) in the H<sub>2</sub>RA group, and 11,089 (3.3%) in the PPI group. Obesity was documented in 11% of the children

who did not receive any of the target medications. In comparison, 15.3% of the children given antibiotics, 15.1% of those given an H<sub>2</sub>RA, and 16.6% of those receiving a PPI developed obesity. The adjusted hazard ratio for H<sub>2</sub>RA use was 1.01 (95% CI 1.00-1.02) and for PPI use was 1.02 (95% CI 1.01-1.03). Use of medications from more than one group increased the association with obesity; and in the patients given acid suppression therapy, the association was stronger with each 30-day supply prescribed.

#### Dose Reduction

It has been suggested that the toxicities seen with PPIs in children may reflect excessive doses and use well beyond the recommended duration of therapy. Current weight-based PPI dosing recommendations have been based on pharmacokinetic and pharmacodynamic studies designed to produce plasma concentrations similar to those of adults receiving standard treatment, which may not represent an appropriate goal for infants and children being treated for GERD or for patients receiving gastric acid suppression as prophylaxis during treatment with non-steroidal anti-inflammatory agents.

The risk for excessive dosing may be heightened in obese children. Several recent papers from Shakhnovich and colleagues, writing for the Best Pharmaceuticals for Children Act Pediatric Trials Network, suggest that obese children require lower doses of pantoprazole than nonobese children to reach effective plasma concentrations.<sup>14-16</sup> In their first paper, the authors conducted a multicenter open-label pharmacokinetic study in 41 obese children and adolescents.<sup>14</sup> The patients, ranging from 6 to 17 years of age, were given a single oral pantoprazole dose of approximately 1.2 mg/kg lean body weight (LBW). All patients had been genotyped for CYP2C19 variants, with the poor metabolizers and ultra-metabolizers excluded from the analysis. Pharmacokinetic parameters were generated using noncompartmental methods and compared to historical data from a previously published study conducted in nonobese patients.

When corrected for a total body weight (TBW)-normalized dose, the apparent clearance (CL/F) and volume of distribution (Vd/F) for pantoprazole were significantly lower in obese children compared to nonobese children (CL/F  $0.23 \pm 0.13$  L/hr/kg versus  $0.42 \pm 0.27$  L/hr/kg,  $p = 0.03$ , and Vd/F  $0.3 \pm 0.1$  L/kg versus  $0.59 \pm 0.36$  L/kg,  $p = 0.008$ ). These changes resulted in significantly greater systemic exposure in the obese patients, as evidenced by higher maximum plasma concentrations ( $3.52 \pm 1.13$  mcg/mL versus  $2.03 \pm 0.92$  mcg/mL,  $p = 0.0001$ ) and area under the concentration-time curve ( $5.82 \pm 3.86$  mcg·hr/mL versus  $3.45 \pm 2.48$  mcg·hr/mL,  $p =$

0.04). When corrected for an LBW-normalized dose, those differences were no longer present in the adolescents and were greatly reduced in the children under 12 years of age.

In a subsequent publication, the group used data from their first study to develop a population-based pharmacokinetic model for pantoprazole dosing in obese children and adolescents.<sup>15</sup> Using NONMEM for model development, they generated a two-compartment model that incorporated CYP2C19 genotype and total body weight. The resulting model was used to evaluate different dosing scenarios. The authors found that the currently approved tiered dosing by weight group for oral pantoprazole (20 mg daily of the delayed-release tablets or granules for suspension in children weighing 15 to 39 kg and 40 mg daily in those weighing 40 kg or greater) achieved the desired drug exposure without the need for additional dose escalation for obese patients.

The most recent publication from the group was a prospective study utilizing weight-based pantoprazole dosing with LBW in obese and nonobese children.<sup>16</sup> Sixty-two children between 6 and 17 years of age were enrolled. All patients received a single dose of pantoprazole 1.2 mg/kg calculated with LBW. Serial plasma concentrations were measured over 8 hours. This method compensated for the 50% lower clearance seen in the children with obesity compared to the nonobese children when dosed using TBW. Use of the recommended 1.2 mg/kg LBW, or the tiered approach in the prescribing information for pantoprazole, should minimize excessive dosing and lessen the risk for adverse effects.

### Summary

Proton pump inhibitors are useful options for the treatment of GERD or gastric bleeding refractory to other treatments. Long-term treatment and high-dose therapy, however, have been linked to a number of serious adverse effects. With new papers describing these risks in infants and children, pediatric healthcare providers are encouraged to carefully consider the role of these in their clinical practice. It is recommended that H<sub>2</sub>RA be considered first-line agents, and that in cases when a PPI is necessary, the lowest effective dose and the shortest treatment duration be used to minimize exposure.

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