Acid Suppression Therapy and Symptom Improvement (or Lack Thereof) in Children

Mary Boruta, MD, Richard Boruta, MD, Jennifer Li, MD

Acid suppression therapy, in the form of histamine H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs), is a common treatment in pediatrics for management of gastroesophageal reflux (GER). Symptoms commonly associated with GER in younger children include frequent emesis, back arching, fussiness, and discomfort. GER symptoms are reported in 10.3% of all children, with symptoms even more commonly noted in individuals <2 years old.[1] At 4 months of age, 67% of children have daily regurgitation. Parents report a perceived problem with GER in 23% of 6-month-old infants.[2] This high rate of concern results in GER being a common complaint in outpatient and inpatient settings. Combined with the ready availability of acid suppression therapy, this has led to increased prescribing of both H_2RAs and PPIs in both infants and older children.[3,4] Acid suppression therapy has been previously viewed as benign; however, recent research has revealed that these medications may carry risk.

In this issue of *Pediatrics*, Malchodi et al[5] assessed possible long-term adverse effects from use of acid suppression therapy. The authors created a database of children to evaluate both the frequency of acid suppressant use and the median age of first bone fracture. An extensive database of 851 631 military dependent children born during a 12-year period was developed by using the Military Healthcare System. Use of this database allowed the authors to identify children <1 year of age prescribed an acid suppressant and any subsequent fracture diagnosis. The authors excluded children with conditions that increased the risk of fractures. Of the studied population, 97 286 (11%) infants were given courses of acid suppression therapy, with 71 578 (73%) given H_2RAs, 7998 (9%) given PPIs, and 17 710 (18%) given a combination of PPIs and H_2RAs.

The authors found an increased childhood fracture hazard ratio (HR) of 23% with PPIs (HR 1.23; 95% confidence interval 1.14–1.31) and of 31% for combination PPIs and H_2RAs (HR 1.31; 95% confidence interval 1.25–1.37) when used at <1 year of age. They discovered no significant increased fracture hazard with H_2RA monotherapy. Furthermore, the study also revealed increased fracture hazard with longer duration of PPI and combination PPI and H_2RA use as well as earlier onset of use of those medications. The fracture hazard was most elevated at 50% with combination PPI and H_2RA use for >338 days.

The argument for pediatric acid suppression therapy has mainly been focused on symptomatic relief of GER disease. Several acid-suppressing drugs have received pediatric exclusivity and an extra 6 months of patent extension for their manufacturers by performing clinical trials in children.[6] However, in infants, multiple studies have failed to show reduction in clinical symptoms of

Department of Pediatrics, School of Medicine, Duke University, Durham, North Carolina

DOI: https://doi.org/10.1542/peds.2019-0909

Accepted for publication Apr 4, 2019

Address correspondence to Mary Boruta, MD, Department of Pediatrics, Duke University Medical Center, DUMC 102375, Durham, NC 27710. E-mail: mary.boruta@duke.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-2625.

To cite: Boruta M, Boruta R, Li J. Acid Suppression Therapy and Symptom Improvement (or Lack Thereof) in Children. *Pediatrics*. 2019;144(1):e20190909

crying, coughing, and back arching with PPIs compared with placebos.[7] Those studies also did not demonstrate improvement in regurgitation in infants with use of PPIs. Trials used to assess H_2RAs have had similar results, with no significant reduction in symptoms of crying in infants when compared with placebos.[7]

Possible complications associated with use of acid suppression therapy have recently been addressed in adult literature, with a focus on PPIs. Possible adverse effects of PPIs include increased risk of chronic kidney disease, bone fracture, dementia, small intestinal bacterial overgrowth, enteric infection, and micronutrient deficiency.[8] Studies addressing specific complications for children are becoming available. In previous articles, pediatric acid suppression therapy has been linked with increased risk for necrotizing enterocolitis, bloodstream infection, pneumonia, and gastroenteritis.[3] In a recent study, use of both H_2RAs and PPIs in the first 2 years of life was linked to obesity in older children.[9]

In their study, Malchodi et al[5] forwarded the conversation on the risk of acid suppression by specifically investigating a link with fractures in children. A previous study by Freedberg et al[10] revealed an association between use of PPIs in individuals <30 years old and increased fractures; however, the authors were unable to establish a PPI-fracture relationship in children. In their study, Malchodi et al[5] furthered our understanding by assessing how acid suppression exposure in infancy, during a period of significant bone development, has an influence on risk.

Investigations revealing a clear link between use of acid suppression medications and adverse effects may necessitate changing of prescribing patterns for these medications in children. This is especially true in the setting of data showing limited clinical improvement with their use. As discussed in recent societal practice guidelines, providers need to collaborate with their patients' families to better understand the risks and benefits of such medications and consider offering nonmedication therapies that may be more beneficial.[7] Studies documenting risk provide an opportunity to reflect on other medications commonly used in pediatrics. Unfortunately, most medications lack robust data on potential harms in children. This deficiency supports national efforts to monitor longer-term adverse effects of new medications brought to the market that are not captured in short-term clinical trials.

ABBREVIATIONS

GER: gastroesophageal reflux
H_2RA: histamine H_2-receptor antagonist
HR: hazard ratio
PPI: proton pump inhibitor

REFERENCES

1. Martigne L, Delaage PH, Thomas-Delecourt F, Bonnelye G, Barthélémy P, Gottrand F. Prevalence and management of gastroesophageal reflux disease in children and adolescents: a nationwide cross-sectional observational study. *Eur J Pediatr*. 2012;171(12):1767–1773
2. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med*. 1997; 151(6):569–572
3. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Neonatal histamine-2 receptor antagonist and proton pump inhibitor treatment at United States children's hospitals. *J Pediatr*. 2016;174: 63–70.e3
4. Illueca M, Alemayehu B, Shoetan N, Yang H. Proton pump inhibitor prescribing patterns in newborns and infants. *J Pediatr Pharmacol Ther*. 2014;19(4): 283–287
5. Malchodi L, Wagner K, Susi A, Gorman G, Hisle-Gorman E. Early acid suppression therapy exposure and fracture in young children. *Pediatrics*. 2019;144(1): e20182625
6. US Food and Drug Administration. Approved active moieties to which FDA has issued a written request for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act. 2018. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM514985.pdf. Accessed March 14, 2019
7. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018; 66(3):516–554
8. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology*. 2017;153(1): 35–48
9. Stark CM, Susi A, Emerick J, Nylund CM. Antibiotic and acid-suppression medications during early childhood are associated with obesity. *Gut*. 2019;68(1): 62–69
10. Freedberg DE, Haynes K, Denburg MR, et al. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. *Osteoporos Int*. 2015;26(10): 2501–2507

Acid Suppression Therapy and Symptom Improvement (or Lack Thereof) in Children

Mary Boruta, Richard Boruta and Jennifer Li

Pediatrics 2019;144;
DOI: 10.1542/peds.2019-0909 originally published online June 7, 2019;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Acid Suppression Therapy and Symptom Improvement (or Lack Thereof) in Children

Mary Boruta, Richard Boruta and Jennifer Li

Pediatrics 2019;144;
DOI: 10.1542/peds.2019-0909 originally published online June 7, 2019;