Use of Reflux Medications in Premature Infants After Hospital Discharge

P. Brian Smith, MD, MPH, MHS

Medications are frequently used to treat gastroesophageal reflux (GER) in premature infants.[1–4] However, diagnostic modalities for GER are poor and clinical diagnosis is highly variable. Like all medications, GER medications have side effects specific to their drug class. In addition, a number of these medications have been associated with significant harm (eg, sepsis, necrotizing enterocolitis [NEC]) in large cohort studies.[2,5–7]

In this issue of *Pediatrics*, D'Agostino et al use an electronic health record from 30 sites in Pennsylvania and New Jersey to document the use of GER medications in infants ≤35 weeks' gestation at birth born between January 2005 and January 2009.[8] They find that 37% (812 of 2217) of the cohort was treated with GER medications in the first year of life. Strikingly, in >75% of cases, these medications were started after the initial presentation to the ambulatory setting. The length of exposure to these medications was prolonged: 375 days (interquartile range: 165–515) for infants started on therapy in the NICU and 294 days (interquartile range: 117–359) for those started on medications after NICU discharge.

Despite the frequent use of GER medications in premature infants, short- or long-term benefits of GER medications in this population are undocumented. Studies in premature infants have failed to show a correlation between apnea, bradycardia, or respiratory symptoms typically thought to be due to GER. In a small, blinded, placebo-controlled, crossover trial of metoclopramide and ranitidine in premature infants, bradycardic episodes worsened with treatment.[9] Two studies evaluating the efficacy of proton pump inhibitors in infants found no difference in efficacy between the study drug and placebo.[10–12]

Low gastric pH may be protective against development of infections and NEC in premature infants. Antacids significantly increase gastric pH, thus inhibiting the premature gut's natural defense against bacterial growth. Histamine-2 (H2) receptor blocker–induced alterations to the fecal microbiota of premature infants lower microbial diversity and promote overgrowth of Proteobacteria.[13] These alterations weaken the gastrointestinal tract's protective barrier and render very low birth weight (VLBW) infants, already predisposed to NEC and other infections, even more vulnerable. Use of H2 receptor blocker medications, the most commonly used GER medications in premature infants,[3] increased the risk of NEC in a cohort of 11 000 VLBW (<1500 g birth weight) infants (odds ratio = 1.71; 95% confidence interval 1.34–2.19).[5] Infants receiving antacid therapy are also at increased risk of bacteremia, lower respiratory tract infections, aspiration pneumonia, and death.[1,5,6,14] In a cohort of >127 000 VLBW infants from >300 NICUs, we observed a similar association between H2 blocker therapy and the combined outcome of death, NEC, or sepsis.[2]

Duke University Medical Center, Durham, North Carolina

DOI: 10.1542/peds.2016-2849

Accepted for publication Sep 13, 2016

Address correspondence to P. Brian Smith, MD, MPH, MHS, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail: brian.smith@duke.edu

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

FINANCIAL DISCLOSURE: Dr Smith receives salary support for research from the National Institutes of Health (NIH) and the National Center for Advancing Translational Sciences of the NIH (grants 1R21HD080606-01A1 and UL1TR001117), the National Institute of Child Health and Human Development (grants HHSN275201000003I and 1R01-HD081044-01), and the US Food and Drug Administration (grant 1R18-FD005292-01). He is a consultant for Astellas Pharma and Abbvie and receives grant support from Cempra Pharmaceuticals (subaward to HHS0100201300009C) and Shionogi. He receives industry support for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

FUNDING: Dr Smith receives salary support from the National Institutes of Health (grants 1R21HD080606-01A1, UL1TR001117, HHSN275201000003I, and 1R01-HD081044-01) and the US Food and Drug Administration (1R18-FD005292-01). Funded by the National Institutes of Health (NIH).

To cite: Smith PB. Use of Reflux Medications in Premature Infants After Hospital Discharge. *Pediatrics.* 2016;138(6):e20162849

GER medications were once widely used in premature infants hospitalized in the NICU.[4] Dramatic inconsistency of treatment practices were observed among the National Institute of Child Health and Human Development Neonatal Research Network NICUs; medical treatment of GER among extremely low birth weight (<1000 g birth weight) infants at discharge ranged from 2% to 90%.[1] Because of the lack of evidence of benefit and the increasing evidence of harm, quality improvement efforts in NICUs have focused on reducing the use of these medications. These efforts to reduce H2 blocker exposure in the NICU have been successful, as evidenced by a decline in use from 23% in 2005 to 8% in 2012.[2,15] However, the data from D'Agostino et al suggest that the majority of infant exposure to GER medications occurs after hospital discharge and, in fact, is often initiated in the outpatient setting.[8]

Pediatrics has a long history of widespread use of medications for which the risks did not outweigh the benefits. All drugs should be shown to be both safe and effective before use. The study by D'Agostino has documented widespread, long-term use of medications that are likely neither.

ABBREVIATIONS

GER: gastroesophageal reflux
H2: histamine-2
NEC: necrotizing enterocolitis
VLBW: very low birth weight

POTENTIAL CONFLICT OF INTEREST: Dr Smith is a consultant for Astellas Pharma and Abbvie and receives grant support from Cempra Pharmaceuticals and Shionogi.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2016-1977.

REFERENCES

1. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM; National Institute of Child Health and Human Development Neonatal Research Network. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics*. 2008;121(1):22–27
2. Romaine A, Ye D, Ao Z, et al; Best Pharmaceuticals for Children Act – Pediatric Trials Network. Safety of histamine-2 receptor blockers in hospitalized VLBW infants. *Early Hum Dev*. 2016;99:27–30
3. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK Jr, Smith PB; Best Pharmaceuticals for Children Act—Pediatric Network. Medication use in the neonatal intensive care unit. *Am J Perinatol*. 2014;31(9):811–821
4. 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.e63
5. Guillet R, Stoll BJ, Cotten CM, et al; National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;117(2). Available at: www.pediatrics.org/cgi/content/full/117/2/e137
6. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012;129(1). Available at: www.pediatrics.org/cgi/content/full/129/1/e40
7. Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. *Pediatrics*. 2006;118(2):746–752
8. D'Agostino JA, Passarella M, Martin AE, Lorch SA. Use of gastroesophageal reflux medications in premature infants after NICU discharge. *Pediatrics*. 2016;138(6):e20161977
9. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009;155(4):516–521
10. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr*. 2009;154(4):514–520.e514
11. Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr*. 2013;163(3):692–698
12. Chen I-L, Gao W-Y, Johnson AP, et al. Proton pump inhibitor use in infants: FDA reviewer experience. *J Pediatr Gastroenterol Nutr*. 2012;54(1):8–14
13. Gupta RW, Tran L, Norori J, et al. Histamine-2 receptor blockers alter the fecal microbiota in premature infants. *J Pediatr Gastroenterol Nutr*. 2013;56(4):397–400
14. Bilali A, Galanis P, Bartsocas C, Sparos L, Velonakis E. H2-blocker therapy and incidence of necrotizing enterocolitis in preterm infants: a case-control study. *Pediatr Neonatol*. 2013;54(2):141–142
15. Ellsbury DL, Ursprung R. A quality improvement approach to optimizing medication use in the neonatal intensive care unit. *Clin Perinatol*. 2012;39(1):1–10

Use of Reflux Medications in Premature Infants After Hospital Discharge

P. Brian Smith

Pediatrics 2016;138;
DOI: 10.1542/peds.2016-2849 originally published online November 23, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Use of Reflux Medications in Premature Infants After Hospital Discharge

P. Brian Smith

Pediatrics 2016;138;
DOI: 10.1542/peds.2016-2849 originally published online November 23, 2016;