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Safety of Histamine-2 Receptor Blockers in Hospitalized VLBW Infants

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Abstract

Background—Histamine-2 receptor (H₂) blockers are often used in very low birth weight infants despite lack of population specific efficacy and safety data.

Aims—We sought to describe safety and temporal trends in histamine-2 receptor (H₂) blocker use in hospitalized very low birth weight (VLBW) infants.

Study Design—We conducted a retrospective cohort study using a clinical database populated by an electronic health record shared by 348 neonatal intensive care units in the United States.

Subjects—We included all VLBW infants without major congenital anomalies.

Outcome Measures—We used multivariable logistic regression with generalizing estimating equations to evaluate the association between days of H₂ blocker exposure and risk of: 1) death or necrotizing enterocolitis (NEC); 2) death or sepsis; and 3) death, NEC, or sepsis.

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Results—Of 127,707 infants, 20,288 (16%) were exposed to H₂ blockers for a total of 6,422,352 days. Median gestational age for infants exposed to H₂ blockers was 27 weeks (25th 75th percentile 26, 29). H₂ blocker use decreased from 18% of infants in 1997 to 8% in 2012 ($p<0.001$). On multivariable analysis, infants were at increased risk of the combined outcome of death, NEC, or sepsis on days exposed to H₂ blockers (odds ratio = 1.14 (95% confidence interval 1.08, 1.19).

Conclusions—H₂ blocker use is associated with increased risk of the combined outcome of death, NEC, or sepsis in hospitalized VLBW infants.

Keywords

histamine-2 receptor antagonists; H₂ blockers; infants; necrotizing enterocolitis

INTRODUCTION

Histamine-2 receptor (H₂) blockers are often used in very low birth weight (VLBW) infants (<1500 g birth weight) to improve gastric reflux by suppressing gastric acid production.(1, 2) H₂ blockers used in the neonatal intensive care unit (NICU) have included cimetidine, famotidine, and ranitidine.(2) Multiple efficacy trials in term infants and older children have shown H₂ blockers improve gastric reflux symptoms and reduce esophageal acid exposure and inflammation with an overall favorable safety profile.(3-10) These findings, however, have not been reproduced in VLBW infants.(1)

Retrospective case control studies and prospective cohort studies have reported frequent use of H₂ blocker therapy in VLBW infants, and associated it with increased risk of necrotizing enterocolitis (NEC), infection, and death, but are limited by small sample sizes, restriction to academic medical centers, and/or lack of reporting trends in medication use over time. (11-14) We used a large multicenter electronic medical record derived database to describe temporal trends in H₂ blocker use in VLBW infants, and explore its association with death, NEC, or sepsis.

MATERIAL AND METHODS

Data Source and Study Cohort

We obtained data from the Pediatrix Medical Group Clinical Data Warehouse (CDW), which prospectively captures information from an electronic medical record shared by 348 North American NICUs. Information from daily progress notes and other electronic documentation is entered into the CDW for quality assurance and research purposes.(15) We included all VLBW infants who were discharged between 1997 and 2012, and were exposed to at least one day of therapy with a H₂ blocker while hospitalized in the first 120 days of life. We excluded infants with major congenital anomalies.

Definitions

We defined days of H₂ blocker exposure as exposure to ranitidine, cimetidine, or famotidine from the first day of therapy through 7 days after discontinuation of the drug. We defined sepsis as positive blood culture for organisms not typically considered contaminants, and NEC as diagnosed by the treating provider. We defined small for gestational age (SGA)

status as previously described.(16) We defined daily exposure to inotropes (dobutamine, dopamine, epinephrine, milrinone), mechanical ventilation, and supplemental oxygen (fraction of inspired oxygen (FiO_2)>21%) as any exposure to these supportive measures during a day of hospitalization. We defined neutropenia as an absolute neutrophil count <500 cells/ μL and nil per os (NPO) status as lack of formula or maternal breast milk administration on a day of hospitalization. We considered infants exposed to H_2 blockers on the last day of hospitalization as being discharged on the drug.

Statistical Analysis

The unit of observation for this analysis was an infant-day of hospitalization. We used standard summary statistics to describe all study variables. We compared distributions of these variables between infants exposed and those not exposed to H_2 blockers using Chi square tests of association or, where appropriate, Wilcoxon rank sum tests. We created 3 separate multivariable logistic regression models to evaluate the association between H_2 blocker exposure and: 1) death or NEC; 2) death or sepsis; and 3) death or NEC or sepsis on each infant day of hospitalization. Our final model included the following covariates: gestational age (categorical variable), SGA status (binary variable), exposure to inotropes on this day (binary variable), exposure to mechanical ventilation on this day (binary variable), highest FiO_2 on this day (categorical), neutropenia on this day, NPO status on this day, postnatal age in days (continuous variable), and discharge year (continuous variable). We generalized estimating equations to account for the clustered nature of the data by infant, and reported odds ratios with 95% confidence intervals from the regressions. All analyses were conducted using STATA 14 (College Station, TX), and we considered a p-value <0.05 statistically significant. This study was approved by the Duke University Institutional Review Board with a waiver of written informed consent.

RESULTS

We identified 127,707 VLBW infants—20,288 (16%) exposed to H_2 blockers for a total of 6,422,352 days. The median postnatal age at first exposure to H_2 blockers and median duration of exposure for those infants ever exposed to the drug were 24 days [25th, 75th percentile 9, 47] and 10 days [3, 23], respectively. Infants exposed to H_2 blockers were less mature and of lower birth weight compared to those not exposed, 27 weeks, [26, 29] versus 29 weeks, [26, 31], $p<0.001$ and 950 g, [750-1190] versus 1120 g, [840-1332], $p<0.001$) (Table 1). The proportion of VLBW infants exposed to H_2 blockers decreased from 18% of infants in 1997 to 8% in 2012 ($p<0.001$ from Cochran Armitage trend test) (Figure 1). Similarly, median duration of exposure to H_2 blockers among infants ever exposed to the drug decreased from a peak of 18 days [9, 35] in 1997 to 5 days [1, 12] in 2012.

Of 127,707 VLBW infants, 8130 (6%) developed NEC, 16,692 (13%) developed sepsis, and 11,376 (9%) died. Infants exposed to H_2 blockers were more likely to suffer from all three outcomes analysed: death or NEC, death or sepsis, and death or NEC or sepsis (Table 2). Among infants exposed to H_2 blockers, median duration of exposure was longer for infants who suffered the combined outcome of death or NEC or sepsis compared to those who did not [12 days (4, 27) vs. 10 days (4, 23), $p<0.001$]. In multivariable analysis, the adjusted

odds of the combined outcome of death or NEC or sepsis were significantly higher on days with exposure to H₂ blockers (odds ratio [OR] = 1.14, 95% confidence interval [95% CI] 1.09-1.20) (Table 3). Further, mirroring the decline in H₂ blocker exposure over time, there was a trend towards decreasing proportion of infants suffering from death or NEC (2.6% in 1996 to 1.5% in 2012), death or sepsis (3.8% in 1997 to 2.4% in 2012), and death or NEC or sepsis (3.8% in 1997 to 2.6% in 2012), though only the decline in death or NEC reached statistical significance ($p=0.02$ from Cochrane Armitage trend test). The adjusted odds ratio for death or NEC and death or sepsis alone however did not reach statistical significance. In a sensitivity analysis limiting exposure through 3 days after discontinuation of the drug, the association between H₂ blocker exposure and odds of death or NEC or sepsis was similar (OR=1.14, 95% CI 1.09, 1.20). Among 17,303 survivors ever exposed to H₂ blockers, 1738 (10%) were discharged home on an H₂ blocker. The prevalence of H₂ blocker at discharge rose from 11% in 1997 to 23% in 2005, but has since declined to 8% in 2012 ($p<0.001$ from Cochrane Armitage trend test)

DISCUSSION

We conducted the largest study of hospitalized VLBW infants exposed to H₂ blockers. We found that infants exposed to the drugs were at increased risk of death, NEC, or sepsis. While H₂ blocker use in this population has declined steadily since 2005, 8% of infants remain exposed to the drug.

Recent observational studies raised concerns about the safety profile of H₂ blockers, particularly in premature infants. A prospective, observational study of 274 VLBW infants from 4 European NICUs found that those exposed to ranitidine during their hospitalization were at greater risk for NEC (9.8% versus 1.6%, $p=0.003$) and sepsis (25.3% versus 8.7%, $p<0.001$) and had higher mortality (9.9% versus 1.6%, $p=0.003$).⁽¹³⁾ Similar findings were presented in an observational study of 11,936 VLBW infants at one of the 19 *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD) Neonatal Research Network centers (1998 to 2001), which reported a significant association between treatment with H₂ blockers and a higher incidence of NEC ($p<0.001$).⁽¹¹⁾ Our study yielded similar results, strengthened by a larger population of infants and an analysis of day-level H₂ blocker exposure that previous studies lacked, but limited by its retrospective nature to a description of association only.

H₂ blockers and other antacids significantly increase gastric pH, thus inhibiting the premature gut's natural defense against bacterial growth. Gupta et al. observed that H₂ blocker-induced alterations to the fecal microbiota include lowered microbial diversity and overgrowth of Proteobacteria. These alterations weaken the gastrointestinal tract's protective barrier, and may leave vulnerable VLBW infants predisposed to NEC.⁽¹⁷⁾

We observed a decline in H₂ blocker use from 23% in 2005 to 8% in 2012. This trend is consistent with the timeline of literature reports: adverse effects of H₂-blocker therapy in adults were first described in the 1990s, but it was not until the early 2000s that studies reported on the safety of these drugs in premature infants. A 2006 study from the National Institute of Child Health and Human Development Neonatal Research Network was among

the first publications to report an association between H₂-blocker therapy and NEC in VLBW infants.(11) In 2009, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition published clinical practice guidelines for pediatric gastroesophageal reflux, which warned of H₂ blockers' association with NEC and presented them as inferior to proton pump inhibitors (PPIs).(19)

Despite the decline in exposure, neonatologists continue to express concern about overuse of H₂ blockers in the treatment of infant gastro-oesophageal reflux disease, both in the NICU and at time of discharge. A 2012 quality-improvement assessment of NICU medication use, citing the adverse effects of anti-reflux medications, advised an educational intervention to "create acceptance for stopping use of what was previously considered to be a safe and effective therapy."(18) Our data suggest that these recommendations are generally reflected in the trajectory of clinical practice in the neonatology community during the past decade, although some outliers remain. Even in 2012, the year with the lowest overall use of H₂ blockers, >50% of VLBW infants were exposed to the drug at 2 sites. Whether or not other practices at high H₂ blocker use sites are associated with worse outcomes is not known. It is also concerning that H₂ blocker therapy in the NICU may translate to use of the drugs after discharge, as was the case for 1 in 10 infants in our study.

Alternative pharmacological strategies for treating infant gastroesophageal reflux disease include PPIs and prokinetic therapy.(19) A 2014 Cochrane review found moderate evidence to support the use of PPIs over H₂ blockers in the treatment of pediatric gastroesophageal reflux, but noted the difficulty in drawing conclusions due to a lack of placebo-controlled trials, especially in infants.(20) Prokinetics previously studied in infants include erythromycin and metoclopramide, but neither are approved for this use by the Food and Drug Administration and both have serious potential side effects including pyloric stenosis and dopaminergic dysregulation.(19-23)

The primary strength of our study is its large and diverse study population; it is the largest study to date examining H₂ blockers in VLBW infants. The Pediatrix CDW includes data from 348 US NICUs ranging from community settings to academic medical centers.(15) We were further able to examine day-level exposure to H₂ blockers, as well as trends in H₂ blocker use over time, demonstrating the success of efforts aimed at reducing exposure in VLBW infants. Limitations of this study stem primarily from its use of electronic medical record-based data, which has not undergone the scrutiny of prospectively collected data including verification of source documents. Due to a lack of randomization, we are limited to a description of associations between drug exposure and outcomes, and do not infer causality. For example, the lower GA of infants exposed to H₂ blockers may have predisposed them to worse outcomes, which may have biased our findings despite the inclusion of GA in the multivariable regression. In addition, while we did have access to days of exposure to H₂ blockers, the database provided no information on indication, dosing amount, and dosing interval, limiting our ability to quantify an infant's drug exposure and relate it to safety events. We were also not able to identify potential rare diagnoses where H₂ blocker therapy may be indicated in this patient population. Other covariates associated with the outcomes analysed including patent ductus arteriosus diagnosis, or presence of a central

venous line were not available for inclusion in the regression, nor were details on enteral nutrition beyond NPO status. Further lack of detailed description of sites precluded any in depth analysis of site specific effects.

In this cohort of VLBW infants, we observed association between H₂ blocker exposure and morbidities and mortality. While analysis over time shows decreased use of H₂ blockers, these infants continue to receive this drug despite lack of proven efficacy and known safety concerns. Our findings support the continued efforts to minimize H₂ blocker exposure in VLBW infants.

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Summary

Using a multicenter electronic health record based clinical database, we characterized histamine-2 receptor (H₂) blocker use in very low birth weight (VLBW) infants. We found that despite decreasing use over time, VLBW infants frequently remained exposed to H₂ blockers and that exposure was associated with increased morbidity and mortality.

Figure 1.
Temporal trend in H₂ blocker use in very low birth weight infants

Table 1

Demographics

	Any H ₂ -blocker use N=20,288 (%)	No H ₂ -blocker use N=107,419 (%)	P-value*
Gestational age (weeks)			<0.001
25	5054 (25)	19,372 (18)	
26-28	8776 (43)	32,758 (31)	
29-31	6020 (30)	46,545 (43)	
>32	426 (2)	8693 (8)	
Birth weight (g)			<0.001
750	5132 (25)	19,296 (18)	
751-1000	6219 (31)	22,533 (21)	
1001-1500	8937 (44)	65,590 (61)	
Male	10,988 (54)	53,781 (50)	<0.001
Inborn	16,161 (81)	89,833 (84)	<0.001
Caesarean section	14,270 (71)	76,561 (72)	0.001
5-minute Apgar			<0.001
0-3	944 (5)	996 (5)	
4-6	3674 (18)	16,535 (16)	
7-10	15,257 (77)	83,395 (79)	
Race/ethnicity			0.001
White	9410 (48)	49,069 (47)	
Black	5149 (26)	28,167 (27)	
Hispanic	4074 (21)	20,569 (20)	
Other	1020 (5)	5661 (5)	

* all p-values are from Chi square tests of association comparing the distribution of each demographic variable in infants exposed vs. not exposed to H₂ blockers.

Table 2Morbidity and mortality associated with number of infants exposed to H₂ blockers

Outcome	H₂-blocker N=20,288 (%)	No H₂-blocker N=107,419 (%)	P-value
Death or NEC *	3,176 (16)	14,279 (13)	<0.001
Death or sepsis	5,033 (25)	18,787 (17)	<0.001
Death, NEC, or sepsis	6,429 (32)	21,714 (20)	<0.001

*
NEC, necrotizing enterocolitis

Table 3

Adjusted odds of morbidity and mortality from multivariable regression

Adjusted Odds Ratio (95% Confidence Interval)				
	Death or NEC	Death or sepsis	Death, NEC, or sepsis	
H ₂ -blocker	0.96 (0.90, 1.03)	1.01 (0.95, 1.07)	1.14 (1.09, 1.20)	
Gestational age (weeks)				
26-28	0.66 (0.64, 0.69)	0.65 (0.63, 0.67)	0.72 (0.70, 0.74)	
29-32	0.59 (0.55, 0.62)	0.45 (0.43, 0.47)	0.56 (0.53, 0.58)	
>32	0.54 (0.47, 0.63)	0.34 (0.30, 0.39)	0.41 (0.36, 0.46)	
SGA status	1.16 (1.12, 1.21)	1.13 (1.09, 1.17)	1.10 (1.06, 1.13)	
Inotropic support	1.91 (1.83, 1.99)	1.58 (1.52, 1.63)	1.62 (1.57, 1.68)	
Mechanical ventilation	3.81 (3.62, 4.00)	3.14 (3.02, 3.26)	3.04 (2.94, 3.14)	
Highest FiO ₂ (%)				
>21 – 30	0.95 (0.90, 1.01)	1.49 (1.43, 1.56)	1.39 (1.34, 1.44)	
>30	2.56 (2.44, 2.68)	2.80 (2.69, 2.92)	2.37 (2.29, 2.45)	
Neutropenia	4.61 (4.17, 5.09)	4.78 (4.38, 5.23)	5.07 (4.67, 5.50)	
NPO	3.60 (3.45, 3.76)	2.01 (1.94, 2.07)	2.06 (2.01, 2.12)	
Postnatal age (days)	0.98 (0.98, 0.99)	0.98 (0.98, 0.98)	0.98 (0.98, 0.99)	
Discharge year	1.08 (0.92, 1.26)	0.91 (0.80, 1.03)	0.95 (0.85, 1.07)	

NEC, necrotizing enterocolitis; SGA, small for gestational age; FiO₂, fraction of inspired oxygen; NPO nil per os