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Safety of histamine-2 receptor blockers in hospitalized VLBW infants

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ABSTRACT

Background: Histamine-2 receptor (H_2) 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 (H_2) 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 H_2 blocker exposure and risk of: 1) death or necrotizing enterocolitis (NEC); 2) death or sepsis; and 3) death, NEC, or sepsis.
Results: Of 127,707 infants, 20,288 (16%) were exposed to H_2 blockers for a total of 6,422,352 days. Median gestational age for infants exposed to H_2 blockers was 27 weeks (25th 75th percentile 26, 29). H_2 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 H_2 blockers (odds ratio = 1.14) (95% confidence interval 1.08, 1.19).
Conclusions: H_2 blocker use is associated with increased risk of the combined outcome of death, NEC, or sepsis in hospitalized VLBW infants.

1. Introduction

Histamine-2 receptor (H_2) 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]. H_2 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 H_2 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 H_2 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 H_2 blocker use in VLBW infants, and explore its association with death, NEC, or sepsis.

2. Material and methods

2.1. 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.

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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 H_2 blocker while hospitalized in the first 120 days of life. We excluded infants with major congenital anomalies.

2.2. Definitions

We defined days of H_2 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.

2.3. 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.

3. 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 Cochrane Armitage trend test) (Fig. 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 H2 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 H_2 blockers (odds ratio [OR] = 1.14, 95% confidence interval [95% CI] 1.09–1.20) (Table 3). Further, mirroring the decline in H_2 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 H_2 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 H_2 blockers, 1738 (10%) were discharged home on an H_2 blocker. The prevalence of H_2 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).

4. Discussion

We conducted the largest study of hospitalized VLBW infants exposed to H_2 blockers. We found that infants exposed to the drugs were at increased risk of death, NEC, or sepsis. While H_2 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 H_2 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 H_2 blockers and a higher incidence of NEC

Table 1
Demographics.

	Any H_2-blocker use $N = 20.288$ (%)	No H_2-blocker use $N = 107.419$ (%)	p-Value[a]
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-min Apgar			<0.001
0–3	944 (5)	4996 (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)	

[a] All p-values are from Chi square tests of association comparing the distribution of each demographic variable in infants exposed vs. not exposed to H_2 blockers.