Evaluation of Intravenous Ranitidine on Gastric pH in Critically Ill Pediatric Patients

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OBJECTIVE To determine the dosing regimen of intravenous ranitidine (IVR) most likely to achieve a gastric pH of ≥ 4 in critically ill pediatric patients.

METHODS A retrospective cohort study was designed and included patients younger than 19 years with gastric pH samples taken from a nasogastric tube within 24 hours after a dose of IVR in an intensive care unit. Data collection included patient demographics, clinical variables, IVR dosing, and gastric pH samples. Descriptive statistical analysis and multivariable logistic regression analysis with clustering of patients was performed to determine variables associated with odds of obtaining a pH of ≥ 4 .

RESULTS A total of 628 patients (1356 nasogastric samples) met study criteria (median age 1.3 years [IQR, 0.33, 5.7 years]; 53% male). The IVR dose was 0.90 ± 0.30 mg/kg per dose every 8.1 ± 2.9 hours, and 60.9% of patients ($n = 383$) had a pH ≥ 4 . Patients with a pH value ≥ 4 had gastric pH samples taken earlier after a dose of IVR (6.7 ± 5.0 vs. 5.9 ± 4.7 hours, $p < 0.001$) but had no difference in IVR dose per kilogram (0.88 ± 0.31 vs. 0.88 ± 0.26 , $p = 0.86$) or frequency of dosing (7.9 ± 3.2 vs. 7.9 ± 3.2 hours, $p = 0.89$). A multivariable logistic regression model identified increasing age, decreased kidney function, and decreased time to pH sample after an IVR dose with significantly greater odds of pH ≥ 4 .

CONCLUSIONS The IVR dosing to maintain a gastric pH ≥ 4 in critically ill pediatric patients should occur more frequently than every 8 hours. Gastric pH evaluation may be necessary to assess IVR efficacy.

ABBREVIATIONS CICU, cardiac intensive care unit; IVR, intravenous ranitidine; PICU, pediatric intensive care unit

KEYWORDS intensive care; pediatrics; pH; ranitidine; stress ulcer prophylaxis

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Introduction

The use of histamine receptor 2 antagonists in pediatric intensive care patients is a commonly accepted strategy for the prevention of stress-related gastric ulcers and gastric bleeding.¹ Intravenous ranitidine (IVR) is a commonly used medication for gastric stress ulcer prophylaxis in the pediatric population, and pharmacokinetic data have been generated to identify dosing schemes that will result in acceptable serum concentrations and gastric pH values.^{2–8} Although these data have been useful in guiding dosing, the sample sizes are small, and the studies often fail to account for variables common to the critically ill pediatric patient, such as the use of mechanical ventilation (including oscillatory ventilation or use of inhaled nitric oxide), vasopressor or inotropic medication use, and kidney function. The ability of IVR to maintain a gastric pH ≥ 4 , the goal for prevention of stress-induced bleeding, has been shown to be variable, likely due to myriad potential patient factors that can affect gastric acid production and IVR efficacy.^{8–11} We performed a large retrospective review of IVR in the critically ill pediatric patient in order to

ascertain patient and dosing regimens associated with a goal gastric pH value ≥ 4 .

Methods

A retrospective cohort study was designed and approved by the Baylor College of Medicine and affiliated institutions' Institutional Review Board. The Texas Children's Hospital electronic medical record was queried from January 1, 2011, to December 31, 2017, to identify patients admitted to 1 of the 3 pediatric intensive care units (PICUs) or the cardiac intensive care unit (CICU) in the Texas Children's Hospital integrated network who had received IVR. Patients were included if they received IVR while admitted to 1 of the intensive care units, were younger than 19 years during IVR therapy, and had a gastric pH sample taken from a nasogastric tube within 24 hours after a dose of IVR. It is routine practice in patients admitted to the PICU or CICU at our institution for nursing staff to take periodic gastric acid samples and test them at the bedside in patients who have a nasogastric tube. Samples were excluded if the patient was receiving any other type of acid-neutralizing

Table 1. Patient Demographics

Category (n = 628)	Patient Admissions
Male, n (%)	335 (53.3)
Age, yr, median (IQR)	1.3 (0.33, 5.7)
Mechanical ventilation, n (%)	520 (82.8)
Oscillator, n (%)	18 (2.9)
Inhaled nitric oxide, n (%)	17 (2.7)
Extracorporeal membrane oxygenation, n (%)	6 (0.96)
Continuous renal replacement therapy, n (%)	11 (1.8)
Serum creatinine, mg/dL, median (IQR)	0.30 (0.25, 0.42)
Estimated glomerular filtration rate, mL/min/1.73 m ² , mean ± SD	105 ± 49
Vasopressor/inotropic medication use, n (%)	
Dopamine	49 (7.8)
Epinephrine	72 (11.5)
Milrinone	91 (14.5)
Norepinephrine	35 (5.6)
Vasopressin	44 (7.0)
PRISM III score, median (IQR)	6 (3, 11)

medications prior to or during IVR therapy, including oral or intravenous proton pump inhibitor therapy; if the patient was receiving IVR as part of total parenteral nutrition; or if enteral feeds were received within 12 hours prior to the gastric pH sample because enteral feeds would interfere with accurate measurement of gastric pH.

Data collection included: patient weight (kg), height (cm), sex, age (years), location of patient during IVR therapy (PICU or CICU), serum creatinine (mg/dL), IVR dose and time between doses, nasogastric pH and time of sample, mechanical ventilation (including the use of oscillatory ventilation or inhaled nitric oxide) at time of gastric pH sampling, use of a ventricular assist device or extracorporeal membrane oxygenation, use of continuous renal replacement therapy, intravenous vasopressor/inotropic medication use, and pediatric risk of mortality (PRISM III) scores upon admission to the intensive care unit.¹² Dosing guidelines for IVR at our institution were 0.5 to 2 mg/kg per dose every 6 to 12 hours, with adjustments for renal dysfunction. Gastric pH was measured with MColorpHast pH-indicator strips (EMD Millipore Corporation, Billerica, MA). Estimated glomerular filtration rate was calculated with the bedside Schwartz equation.¹³

Descriptive statistical analysis was performed to characterize the patient population using mean, SD, median, IQR, and percent as appropriate. Graphical analysis was also used to evaluate trends in gastric pH compared with time after dose of IVR. Patient admissions served as the denominator for all calculations. An automated stepwise multivariable logistic regression

analysis with clustering of patients, using a p value of <0.2 for backwards inclusion and a p value of <0.1 for forwards inclusion during the automated building process, was performed to determine variables associated with increased odds of a pH of ≥4. All statistical analysis was performed with Stata IC v.12 (StataCorp, College Station, TX), and a p value of <0.05 was considered statistically significant *a priori*.

Results

A total of 628 patient admissions (1356 nasogastric samples) met study criteria (Table 1). No patients underwent therapy with a ventricular assist device. The PICU admissions comprised 82.9%, and CICUs were 17.0% of the patient population. Dose of IVR was 0.90 ± 0.30 mg/kg per dose, with a mean time between doses of 8.1 ± 2.9 hours. The median number of doses prior to a gastric pH sample was 6 (IQR, 2,15). Patients had a median of 1 nasogastric sample (IQR, 1, 2) at a mean of 5.6 ± 4.1 hours after a dose of IVR. The mean pH value was 3.7 ± 1.5 and, 60.9% of patients (n = 383) had 1 or more pH values ≥4. When graphically evaluated, pH values had a trend toward higher values when proximal to IVR dose (Figure). A total of 409 patients (65.1%) had PRISM III scores calculated (Table 1).

Patients were divided into 2 groups based on a pH value ≥4 at any time (Table 2). Patients with a pH value ≥4 did not have a difference in IVR dose per kilogram (0.88 ± 0.31 vs. 0.88 ± 0.26 mg/kg per dose, p = 0.86) or frequency of dosing (7.9 ± 3.2 vs. 7.9 ± 3.2 hours, p = 0.89), but had more nasogastric samples obtained (1 [1, 2] vs. 2 [1, 3], p < 0.001), had more doses given prior to

Figure. Gastric pH values by time after a dose of intravenous ranitidine. There is trend towards higher gastric pH values proximal to the dose of ranitidine.

the pH sample (4 [2, 8] vs. 5 [2, 10], $p = 0.04$), and had gastric pH samples taken earlier after a dose of IVR (5.9 ± 4.7 vs. 6.7 ± 5.0 hours, $p < 0.001$; Table 2).

A multivariable logistic regression model was developed with clustering around patients ($n = 628$) to determine variables associated with a pH value ≥ 4 in patients receiving IVR. A total of 1356 nasogastric samples were included in the clustered regression analysis, and 47.4% ($n = 642$) of these values were ≥ 4 . Variables significant for an increased odds of a pH ≥ 4 included increasing age and obtaining a pH sample within a shorter time after an IVR dose. An increasing PRISM III score on admission was associated with a greater odds of a pH ≥ 4 , whereas an increasing estimated glomerular filtration rate was associated with a decreased odds of a pH ≥ 4 (Table 3).

Discussion

This is the largest evaluation of IVR for the prophylaxis of stress-related gastric ulcers in the pediatric intensive care population. We chose to evaluate the efficacy of IVR retrospectively to incorporate variables common to patients admitted to the pediatric intensive care unit and to assess their influence on gastric pH and IVR efficacy. There are several points to be made from these data that could potentially influence the practice of gastric stress ulcer prophylaxis in the pediatric intensive care population.

Approximately two-thirds of our study population

had a gastric pH ≥ 4 at some point, which would suggest that the dosing regimen most often used in the current data set, 1 mg/kg per dose approximately every 8 hours as reflected in the data, does not appear to be adequate for a large portion of the pediatric intensive care population. This result also suggests that monitoring of gastric acid pH and titration of dosing in this patient population are warranted, potentially on a daily basis, particularly in the patients at greatest risk for gastric ulcer development, such as those patients with coagulopathies or septic shock.

However, it should be noted that variables such as vasopressor or inotropic medication administration or use of mechanical ventilation, which have been associated with gastric ulcer development, were not strongly associated with an elevated gastric pH while receiving IVR, and patients with a greater PRISM score were more likely to have a lower gastric pH.^{9-11,14-16} It does not appear that variables that increase the risk of gastric stress ulcer development, which are often associated with critical illness, influence the efficacy of IVR in maintaining a pH ≥ 4 .

The most pertinent finding in our analysis is the interval by which IVR should be dosed to have the highest probability of a gastric pH ≥ 4 . As identified in the multivariable logistic regression analysis, each unit increase in time (hours) resulted in a decreased odds of obtaining a pH ≥ 4 . This would suggest that extended dosing intervals of IVR, in patients with normal kidney function, would be less likely to have a pH ≥ 4 . Com-

Table 2. Comparison of Patients With a pH ≥ 4 to Those With a pH < 4

Patients (n = 628)	pH < 4 (n = 245)	pH ≥ 4 (n = 383)	p value
Male, n (%)	134 (54.7)	201 (52.5)	0.62
Age, yr, median (IQR)	0.98 (0.25, 2.8)	1.8 (0.37, 7.9)	< 0.001
Mechanical ventilation, n (%)	206 (84.1)	314 (81.9)	0.52
Oscillator, n (%)	4 (1.6)	14 (3.7)	0.22
Inhaled nitric oxide, n (%)	5 (2.0)	12 (3.1)	0.46
Extracorporeal membrane oxygenation, n (%)	2 (0.82)	4 (1.0)	1.0
Continuous renal replacement therapy, n (%)	3 (1.2)	8 (2.1)	0.54
Serum creatinine, mg/dL, mean $\pm$ SD	0.33 $\pm$ 0.18	0.45 $\pm$ 0.53	< 0.001
Estimated glomerular filtration rate, mL/min/1.73 m ² , mean $\pm$ SD	106 $\pm$ 40	105 $\pm$ 54	0.81
Vasopressor/inotropic medication use, n (%)			
Dopamine	14 (5.7)	35 (9.1)	0.13
Epinephrine	24 (9.8)	48 (12.5)	0.31
Milrinone	46 (18.8)	45 (11.8)	0.02
Norepinephrine	7 (2.9)	28 (7.3)	0.02
Vasopressin	12 (4.9)	32 (8.4)	0.11
PRISM III score, median (IQR)	5 (2, 9)	6 (3, 13)	0.02

mon dosing regimens for IVR include every 6, 8, and 12 hours, and, in keeping with convention, it appears that dosing every 6 hours would be the most efficacious. Prior publications have noted that more frequent dosing intervals, or continuous infusion, are required to maintain goal gastric pH values. A population pharmacokinetic study in critically ill infants noted that doses of 0.7 mg/kg per dose every 6 hours were necessary to maintain gastric pH ≥ 4 .⁸ Similarly, other studies have noted that dosing every 6 hours and/or a continuous infusion of IVR is required to consistently maintain goal gastric pH values in critically ill pediatric patients.^{5,17–19} Based on prior publications and our own analysis, a dosing interval of every 6 hours for bolus dosing of IVR in pediatric critical illness would be necessary to have the highest probability of attainment of a gastric pH ≥ 4 .

We did not identify a difference in attainment of pH ≥ 4 in dose per kilogram of body weight of IVR. Our institutional dosing guideline for IVR is 1 mg/kg per dose every 6 to 8 hours, with adjustments in dose for renal dysfunction. This standard dosing of IVR in our data set makes it difficult to draw conclusions regarding the optimal mg/kg per dose of IVR. Prior publications have noted that higher doses can result in greater likelihood of gastric pH ≥ 4 , with doses of 3 mg/kg/day cited as a minimum effective dose.^{5,19} We would support the conclusion that higher doses are more likely to result in goal gastric pH values. In our analysis, patients with decreased kidney function had a higher probability of a gastric pH ≥ 4 . Intravenous ranitidine is eliminated renally, and patients with a decreased renal function

would be more likely to have a higher serum concentration of ranitidine and greater pH values. Although our analysis cannot make conclusive recommendations regarding dose of IVR, we would recommend the minimum effective dose of 3 mg/kg/day with a dosing interval of less than every 8 hours to have higher odds of obtaining goal gastric pH values.

Despite the lack of association of dose per kilogram of body weight for IVR and gastric pH, there was an association with age, because increasing age was associated with a gastric pH ≥ 4 . Younger patients, in particular neonatal and infant patients, could potentially have a greater volume of distribution or clearance associated with critical illnesses unique to this population. However, prior pharmacokinetic studies have not shown significant differences in volume of distribution with increasing age.^{3,5,6,9} This finding should be noted by clinicians and investigated further to determine the etiology of elevated gastric pH values in older critically ill pediatric patients.

The limitations associated with this analysis are those germane to all retrospective evaluations of data collected during the normal course of patient care. The methodology for pH testing of gastric acid samples used paper pH strips, which measure pH in 0.5 increments and have less granularity and accuracy of measurement compared with more invasive methodologies reported previously. The result interpretation and documentation of the pH were the responsibility of the bedside nurse, which encompassed a large group of health care providers and a potentially greater range

Table 3. Clustered Logistic Regression Model for a pH ≥ 4

Patients (n = 628)	Odds Ratio	95% CI	p value
Age (years)	1.07	1.03–1.11	<0.001
pH time after dose (hours)	0.94	0.91–0.98	0.005
PRISM III score	1.04	1.01–1.07	0.03
Estimated glomerular filtration rate	0.99	0.993–0.999	0.03
Doses prior	0.99	0.97–1.00	0.07
Mechanical ventilation	0.68	0.43–1.06	0.09
Milrinone use	2.93	0.77–11.1	0.11
Extracorporeal membrane oxygenation	0.19	0.02–1.52	0.12
Intravenous ranitidine dose (mg/kg per dose)	1.69	0.83–3.4	0.15
Continuous renal replacement therapy	1.78	0.78–4.1	0.17

of error.^{5,6,8,17} Despite this, our results are in concert with these previous studies. Our study reflects the practice of monitoring gastric pH that is common in pediatric intensive care and would likely be used to titrate therapy, as opposed to more invasive monitoring. The patient population, although the largest reported to date, was a convenience sample and did not reflect a highly controlled prospective study group, which would have added rigor to our investigation. The prescription of IVR was under the purview of the attending clinician, which introduces variability and bias into the selection of the patient population. We have also made the assumption, *a priori*, that a goal pH of ≥ 4 is the ideal for prevention of stress-induced gastric ulcers. We did not evaluate whether a patient had any type of adverse event, such as thrombocytopenia, *Clostridium difficile* infection, or a bleeding complication, or developed a gastric ulcer, and the ideal study would evaluate the efficacy of IVR to prevent gastric ulcers in light of potential adverse events.

Conclusions

The use of IVR was able to maintain a gastric pH at 4 or above in most critically ill pediatric patients. Dosing intervals should be every 6 hours to maintain the greatest odds of a gastric pH at or above 4 in this patient population.

ARTICLE INFORMATION

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