CLINICAL INVESTIGATION

The Effects of Increasing Doses of Ranitidine on Gastric pH in Children

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BACKGROUND Ranitidine is widely used for gastroesophageal reflux disease (GERD) in children, but optimal dosing is unclear. We compared effects of weight-based doses of oral ranitidine on gastric pH in children with clinical GERD.

METHODS Children ages 4–11 years with clinical GERD were enrolled in a multi-center prospective randomized study comparing a fixed dose of ranitidine (Zantac 75) with placebo after an overnight fast; gastric pH was measured for 6 h after the fixed dose (Phase 1). Of the six enrollees from our center, four received active drug during Phase 1; 12 h after the fixed dose, these four children received ranitidine 5 mg/kg (maximum 150 mg) and gastric pH was measured for another 6–12 hours (Phase 2). This report details the effects of two dose ranges (Low Dose, < 3 mg/kg/dose, and High Dose, ≥ 3 mg/kg/dose) on gastric pH in children.

RESULTS The four children were 6.9–11.3 years old and weighed 20.4–49.5 kg. The Low Doses were 1.5–2.7 mg/kg; the High Doses were 3–5 mg/kg. Although the mean percentage of time with gastric pH > 4 during the entire 6 hours following dosing was similar after Low and High Dose (50% vs. 57%, NS), during the last two hours of this interval the mean percentage of time with gastric pH > 4 was only 29% for Low Dose vs. 89% for High Dose (P = 0.006). Moreover, during those two hours, none of the Low Doses kept gastric pH above 4 for > 60% of the time, while all of the High Doses kept pH above 4 for > 60% of the time (P = 0.03). In three of four patients who underwent extended (9–12 h) gastric pH monitoring after High Dose ranitidine, gastric pH was above 4 for more than 40% of total time.

CONCLUSIONS Doses of ranitidine ≥ 3 mg/kg/dose may be required for acid suppression lasting beyond 6 hours.

KEYWORDS: ranitidine, gastric pH, gastroesophageal reflux

J Pediatr Pharmacol Ther 2004;9:259-264

INTRODUCTION

Ranitidine is used widely for treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and hypersecretory disorders in both children and adults.[1,2] As a histamine-2 receptor antagonist (H_2RA), it reduces gastric secretion by competitive inhibition of histamine-2 receptors on gastric parietal cells. It has been available by prescription since 1981, and was approved by the Food and Drug Administration (FDA) for nonprescription use in adults in 1995.[3] Although there are no FDA-approved indications for its use in children, ranitidine enjoys immense popularity for off-label use in children for a wide range of acid-peptic disorders, and is known to have an

ABBREVIATIONS: FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; H_2RA, histamine-2 receptor antagonist; OTC, over the counter

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overall excellent safety profile.

Despite its frequent use in children, however, there is insufficient information regarding optimal dosing of ranitidine in this age group. The current published dosing guidelines recommend a ranitidine dose of 1–3 mg/kg of body weight, two to three times daily.[4,5] However, controlling acid suppression has been challenging with these regimens, particularly in neurologically impaired children and in those with chronic lung disorders, sometimes necessitating use of proton pump inhibitors.[6-8] Exploration of more optimal and effective acid suppression strategies using the currently available medicines is needed in children. We undertook this study because of our clinical experience with the inadequacy of currently published dosing regimens, in order to explore the effects of weight-based doses of ranitidine on gastric pH in children.

METHODS

Design

Phase 1. We and others conducted a multi-center, randomized, double blind, placebo-controlled study of children aged 4–11 years with at least two symptoms or signs of acid reflux (irritability with meals, nausea, regurgitation, heartburn, epigastric or chest pain associated with or relieved by eating, vomiting, nocturnal coughing or wheezing, burping/belching, and pain awakening subject at night) for three or more months. All subjects were hospitalized and fasted 6 hours overnight, after which an intra-gastric pH probe was placed and over the counter (OTC) Zantac 75 (Warner-Lambert Consumer Healthcare, Pfizer Inc., Morris Plains, NJ) or placebo was administered orally. This phase was completed at the end of six hours of continuous gastric pH monitoring. The pharmacodynamic and pharmacokinetic results of this multi-center trial (Phase 1) of fixed dose ranitidine (OTC Zantac 75) in these 19 children were reported earlier.[9]

Phase 2. As an add-on to the above study, the six subjects from our center who completed Phase 1 received ranitidine 5 mg/kg orally (maximum dose 150 mg) approximately 12 hours after the dose of OTC Zantac 75 or placebo, having consumed a regular meal in the interim. Gastric pH was then monitored continuously for 6–12 hours. Results pertaining to the four children who received active drug for both doses (i.e., those who had not been blindly assigned to placebo for Phase 1) are presented here. The ranitidine doses are referred to as either Low Dose (< 3 mg/kg/dose) or High Dose (≥ 3 mg/kg/dose).

Exclusion criteria

Children with renal dysfunction (serum creatinine > 2x normal), hepatic enzyme abnormalities (> 2x normal), diagnosis of peptic ulcer disease, gastrointestinal bleeding, surgery of the upper gastrointestinal tract, and those with other significant medical diagnoses were excluded from both phases of the study. Also, children who had used histamine-2 receptor antagonists (H_2RAs), metoclopramide, cisapride, carafate, misoprostol in the 48 hours prior, proton pump inhibitors in the seven days prior, or non-steroidal anti-inflammatory drugs ≥ five times a week in the two weeks prior to study were excluded.

Subjects

Results from the four children, all male, who received paired doses of ranitidine are reported here. Informed consent approved by the institutional review board of Children's Hospital of Pittsburgh was obtained from all participating subjects.

Intragastric pH monitoring

Nasogastric pH probe (Medtronics Synectics, Shoreview, MN) placement was confirmed by recording a consistent pre-treatment gastric pH < 3.0 for 30 minutes on the pH monitor. The data were obtained from the pH values taken at 4-second intervals during both the last 30 minutes of the pre-treatment period in Phase 1 and for the entire pH study period following active dose administration in each phase. All spurious pH values outside the physiological range (< 0.7 or > 8.5) were assumed to be artifacts and were excluded from statistical analyses. Gastric pH values were averaged across subjects and plotted against separate points in time, and as percentage of time during the study that pH > 4.

Statistics

Data are described by their means, medians, and ranges. The efficacy of acid suppression is expressed as the mean percentage of time that gastric pH values were > 4. Chi-square and Student's t test are used to test nominal and continuous variables, respectively, for statistical significance, using a threshold P value of 0.05.

Table 1. Subject Characteristics and Dosing*

Subject #	Age (yr)	Weight (kg)	1st Dose(Phase 1)	2nd Dose(Phase 2)
1	11.2	49.5	1.5 mg/kg (LD*)	3.0 mg/kg (HD)
2	8.2	39.2	1.9 mg/kg (LD)	3.8 mg/kg (HD)
3	7.2	28	2.7mg/kg (LD)	5.0 mg/kg (HD)
4	6.9	20.4	3.7 mg/kg (HD)	4.9 mg/kg (HD)
Median(Range)	7.8 (6.9–11.2)	33.6 (20.4–49.5)	2.3 mg/kg (1.5–3.7)	4.4 mg/kg (3–5)
Mean ± SD	8.3 ± 1.9	34.2 ± 12.7	2.4 ± 0.9	4.1 ± 0.9

LD = Low Dose (< 3 mg/kg/dose).
HD = High Dose (≥ 3 mg/kg/dose).
**Because of the variety of the children's weights, the fixed (75 mg) dose was a High Dose in one child, despite generally being Low Dose. In addition, the 150 mg maximum, combined with the heavy weights for some of the older children, resulted in the weight-based "5 mg/kg" dose actually being < 5 mg/kg of actual weight in most cases.*

RESULTS

The subjects' characteristics and dosing details are presented in Table 1. One subject in Phase 1 and all in Phase 2 belong to the High Dose group; the child with the lowest weight received two high doses. All but one (3.7 mg/kg/dose) of these High Doses were thus administered in the post-prandial state. The three subjects in the Low Dose group were all administered doses in the fasting state.

Gastric pH

The effects of all the individual ranitidine doses on gastric pH are shown in Figures 1A (Low Dose) and 1B (High Dose). The mean percentage of time gastric pH > 4 during the six hours following dosing was 50% with Low Dose compared to 57% with High Dose, which was not statistically significant (Figure 2). However, when this six hour post-dosing period is examined in detail, particularly the final two hours, the mean percentage of time gastric pH > 4 was only 29% in the Low Dose group compared to 89% in the High Dose group (P = 0.006, Figure 3). During the 4–6 h interval, the Low Doses produced a gastric pH > 4 for less than 60% of the study time in contrast to ≥ 60% for all High Doses (P = 0.03). Four subjects (all in the High Dose group) had pH monitoring extending to 9–12 hours after the second ranitidine dose. Three of these four subjects had gastric pH > 4 for more than 40% of time when the total study time was taken into account.

DISCUSSION

Our data suggest that oral ranitidine doses may need to be higher than 3 mg/kg, or that frequency of administration may need to be more often than two or three times daily, or both, to optimize gastric acid suppression and therapy of children with GERD.

Currently recommended (off-label) pediatric oral dosing regimens are 4–6 mg/kg/day in two to three divided doses.[4,5] However, a substantial number of children continue to suffer from GERD symptoms despite maximizing ranitidine doses in accordance with current recommendations. These challenges occur especially in children with neurological or chronic respiratory disorders, and often prompt the "step-up" of therapy from H_2RAs to proton pump inhibitors. Our anecdotal experience with esophageal pH probe studies in children receiving "standard" ranitidine dosing has suggested sub-optimal gastric acid suppression for much of the day. These considerations prompted the present study as an add-on to a multi-center trial.

Clinical efficacy measures for GERD include symptom amelioration and endoscopic or histologic esophagitis healing. Randomized controlled studies in adults with GERD and esophagitis have demonstrated superiority of ranitidine over placebo in symptom relief and healing of the esophageal mucosa.[1,10,11] In children, data are more limited. Although standard recommendations for pediatric ranitidine dosing have often been in the range of 2.5–3 mg/kg/dose twice or thrice daily, The North American Society of Pediatric Gastroenterology and Nutrition recently published guidelines for the management of pediatric GERD recommending a considerably higher dose of 4–10 mg/kg/day orally,[12] based largely on expert opinion because published data are so limited. Cucchiara et al. showed that suppressing gastric acid improved both clinical symptoms and esophagitis, and found the efficacy of high dose ranitidine (20 mg/kg/day, comparable to our dose of 5 mg/kg given at the

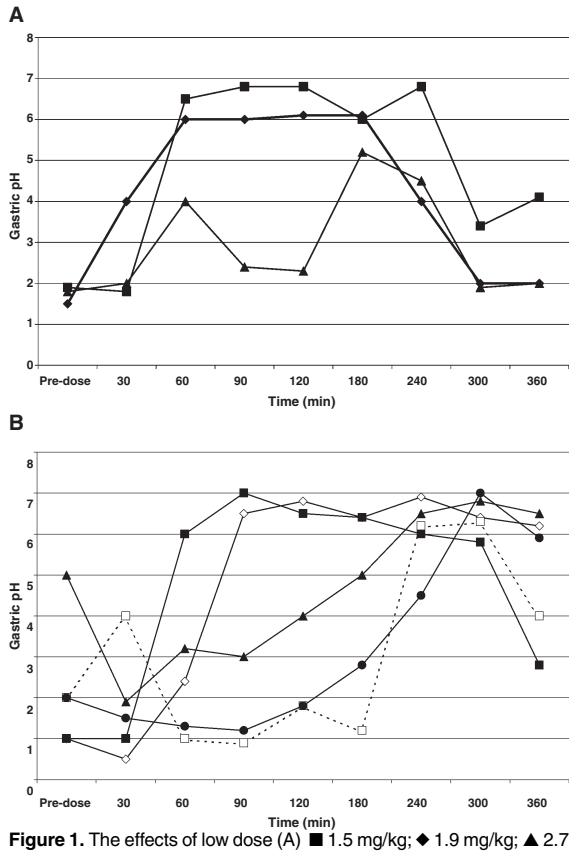

Figure 1. The effects of low dose (A) ■ 1.5 mg/kg; ◆ 1.9 mg/kg; ▲ 2.7 mg/kg, and high dose (B) ranitidine ◇ 3 mg/kg; ■ 3.7 mg/kg; ▲ 3.8 mg/kg; □ 4.9 mg/kg; ◆ 5 mg/kg on gastric pH over a duration of 6 hours post-dose.

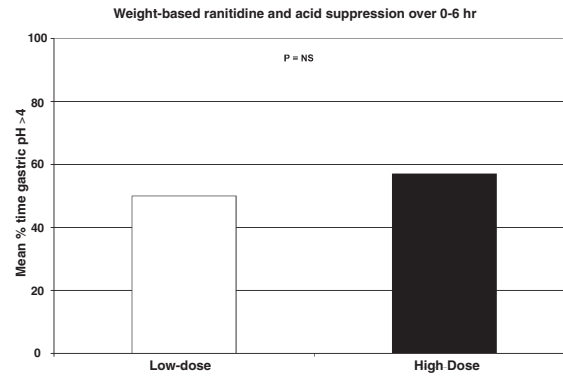

Figure 2. Mean percentage duration of gastric pH > 4 over a duration of 6 hours post-dose in Low Dose versus High Dose ranitidine groups. NS = Not significant.

frequency of every six hours) to be similar to omeprazole (40 mg/1.73m^2/day) during an 8-week treatment trial in 32 children with GERD and esophagitis.[13]

Maintaining esophageal pH above 4 clearly correlates with positive symptomatic, endoscopic, and histologic outcomes, therefore, esophageal pH measurement can be used as a precise and quantitative surrogate for the clinical outcomes of interest.[14-17] Gastric pH studies provide important information about the suppression of gastric acid itself, without the confounding variables of reflux frequency and clearance that affect esophageal pH measurements. Thus, gastric pH measurement provides important pharmacodynamic information regarding the efficacy of anti-secretory medications like ranitidine.[18]

In a study of infants, ranitidine 2 mg/kg/dose administered every eight hours was more effective than 2 mg/kg, 3 mg/kg or even 4 mg/kg administered every 12 hours in terms of total time with gastric pH values < 3 and < 4.[19] In another infant study, ranitidine 5 mg/kg/dose orally increased gastric pH for 9–10 hours.[20] The authors also reported a positive correlation between plasma ranitidine concentration and gastric pH, with gastric pH falling below 4 when the plasma ranitidine level decreased below100 ng/mL, shortly after the ninth hour post-ingestion.

An important study in 12 children aged 3.5–16 years with ulcer disease examined pharmacodynamic and pharmacokinetic responses during six hours of fasting after an oral ranitidine dose. The authors found that serum concentrations of 40–60 ng/mL were required to suppress gastric acid secretion by ≥ 90%. This was generally achieved by the time the ranitidine serum concentration peaked, which occurred on average about two hours after an oral dose; by six hours the average serum concentration dropped below this threshold. The authors concluded with a recommendation of 1.25–1.90 mg/kg orally every twelve hours to suppress acid secretion ≥ 90%, although the relationship between this goal and that required for esophagitis healing is not established, and the effects of ordinary meal ingestion on the pharmacodynamics are not explored.[21]

In the multi-center study that represented Phase 1 of the current single-center study, using a single 75 mg oral dose produced a positive correlation between ranitidine concentration and gastric pH.[9] A substantial decrease in gastric acidity lasted over 5–6 hours.

In our study there was no significant difference in the percentage of total time for gastric pH > 4 between the Low and High Dose groups. In the three recipients of the Low Dose ranitidine in Phase 1 (fasting), pH > 4 was attained within 30–60 minutes post-dose. However, in the High Dose ranitidine group the same effect was seen only

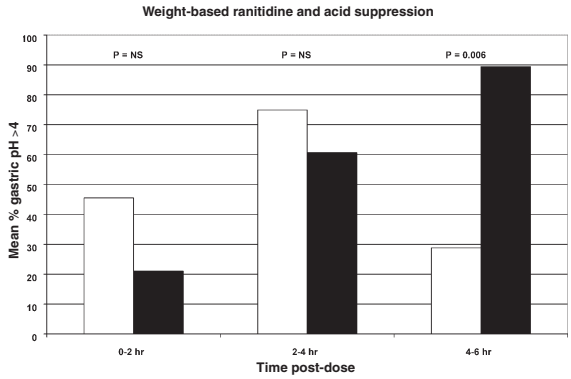

Figure 3. Mean percentage duration of gastric pH > 4 during 0–2 hours, 2–4 hours, and 4–6 hours post-dose in Low Dose and High Dose ranitidine groups. NS = Not significant. □ Low Dose; ■ High Dose.

with the dose administered to the single subject in the fasting state. In the four subjects who received the High Dose in the fed state, the pH rose above 4 after 60–90 minutes in two children and after 180–240 minutes post-dose in the two other children. The delay in attaining a pH above 4 in the latter group probably represents the effect of meal-stimulated increase in acid secretion and may also be due in part to consumption of acidic foods or beverages. In the Low Dose ranitidine group the acid suppressing effect wore off between 4–6 hours, in contrast to the High Dose group, which experienced a significantly greater mean duration of gastric pH above 4 during the 4–6 hour period. During the 4–6 hour time interval post administration, none of the three children administered Low Doses maintained gastric pH above 4 for > 60% of the total time, in contrast to all five children administered High Doses. Moreover, gastric pH above 4 was maintained for > 40% of total study time (9–12 hours) in three subjects who received High Dose ranitidine.

This study is limited by the small number of subjects. It is also limited by the single outcome variable: gastric acidity. Although there is a relationship between esophageal acid suppression and efficacy of GERD treatment, gastric acidity correlates only indirectly with GERD symptom control or esophagitis healing. The study is also confounded by the fasting status of all the Low Doses administered versus the fed status of most of the High Doses, although the consumption of ordinary daily meals is the context in which most clinical administration of oral H_2RAs occurs. All the subjects in this study were boys, but no gender-based differences have been shown in ranitidine pharmacokinetics. No adverse experiences were reported by any of the subjects receiving the two different ranitidine doses in our study.

In conclusion, ranitidine at doses ≥ 3 mg/kg/dose may produce more effective acid suppression beyond four hours after dosing, particularly in the context of ordinary daily meal consumption. A more frequent dosing interval might also be warranted. Questions regarding tolerance[22,23] and compliance with chronic use of more frequent dosing intervals must also be considered. This pilot study suggests the need for further controlled clinical trials of higher or more frequent dosing regimens in larger samples of subjects than are commonly used currently.

DISCLOSURE: The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGMENT: The paper was presented in part as a poster at American Gastroenterological Association Meeting, May 20–23, 2001 in Atlanta, GA.

REFERENCES

1. Pappa KA, Buaron K, Payne JE, Sirgo MA, Giefer EE. An evaluation of increasing doses of ranitidine for treatment of heartburn. Aliment Pharmacol Ther 1999;13:475-81.
2. Cucchiara S, Campanozzi A, Greco L, Franco MT, Emiliano M, Alfieri E, et al. Predictive value of esophageal manometry and gastroesophageal pH monitoring for responsiveness of reflux disease to medical therapy in children. Am J Gastroenterol 1996;91:680-5.
3. Mills JG, Koch KM, Webster C, Sirgo MA, Fitzgerald K, Wood JR. The safety of ranitidine in over a decade of use. Aliment Pharmacol Ther 1997;11:129-37.
4. Siberry GK, Iannone R. The Harriet Lane Handbook, 15th edition. St. Louis, MO: Mosby;2000.
5. Physicians' Desk Reference® 56th edition. Montvale, NJ: Medical Economics Company, Inc.;2002.
6. Kato S, Ebina K, Fujii K, Chiba H, Nakagawa H. Effect of omeprazole in the treatment of refractory acid-related diseases in childhood: endoscopic healing and twenty-four-hour intragastric acidity. J Pediatr 1996;128:415-21.

7. Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. Aliment Pharmacol Ther 2001;15:917-26.
8. Kaufman SS, Loseke CA, Young RJ, Perry DA. Ranitidine therapy for esophagitis in children with developmental disabilities. Clin Pediatr 1996; 35:451-6.
9. Orenstein SR, Blumer JL, Faessel HM, Mcguire JA, Fung K, Li B, et al. Ranitidine 75 mg OTC dose: Pharmacokinetic and pharmacodynamic effects in children with symptoms of gastroesophageal reflux. Aliment Pharmacol Ther 2002;16:899-907.
10. Pappa KA, Gooch WM, Buaron K, Payne JE, Giefer EE, Sirgo MA, et al. Low-dose ranitidine for the relief of heartburn. Aliment Pharmacol Ther 1999;13:459-65.
11. Pappa KA, Williams BO, Payne JE, Buaron KS, Mussari KL, Ciociola AA. A double-blind, placebo-controlled study of the efficacy and safety of non-prescription ranitidine 75 mg in the prevention of meal-induced heartburn. Aliment Pharmacol Ther 1999;13:467-73.
12. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Evaluation and treatment of gastroesophageal reflux in infants and children: An evidence-based review for a clinical guideline. J Pediatr Gastroenterol Nutr 2001;32:S1-31.
13. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux esophagitis. Arch Dis Child 1993;69:655-9.
14. Hunt RH, Cederberg C, Dent J, Halter F, Howden C, Marks IN, et al. Optimizing acid suppression for treatment of acid-related diseases. Dig Dis Sci 1995;40:S24-49.
15. Hunt RH. The relationship between the control of pH and healing and symptom relief in gastroesophageal reflux disease. Aliment Pharmacol Ther 1995;9:3-7.
16. Huang JQ, Hunt RH. pH, healing rate, and symptom relief in patients with GERD. Yale J Biol Med 1999;72:181-94.
17. Hunt RH. Importance of pH control in the management of GERD. Arch Intern Med 1999;159:649-57.
18. Van Herwaarden MA, Samsom M, Smout AJ. 24-h recording of intragastric pH: technical aspects and clinical relevance. Scand J Gastroenterol 1999;230:9-16.
19. Sutphen JL, Dillard VL. Effect of ranitidine on twenty-four-hour gastric acidity in infants. J Pediatr 1989;114:472-4.
20. Mallet E, Mouterde O, Flipo JL, Moore N. Use of ranitidine in young infants with gastroesophageal reflux. Eur J Clin Pharmacol 1989;36:641-2.
21. Blumer JL, Rothstein FC, Kaplan BS, Yamashita TS, Eshelman FN, Myers CM, et al. Pharmacokinetic determination of ranitidine pharmacodynamics in pediatric ulcer disease. J Pediatr 1985;107:301-6.
22. Wilder-Smith CH, Merki HS. Tolerance during dosing with H2-receptor antagonists. An overview. Scand J Gastroenterol 1992;193 Suppl:14-9.
23. Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. Am J Gastroenterol 2000;95:57-61.