JPPT

CLINICAL INVESTIGATION

Comparison of Pantoprazole, Omeprazole and Ranitidine in Children Requiring Acid Suppression: A Prospective Pilot Study

Claire E. Cuttica, PharmD,[1] Michael F. Chicella, PharmD,[2] Dawn E. Butler, PharmD,[3] and Ajay Kaul, MD[4]

[1]Department of Pharmacy, Cook Children's Medical Center, Fort Worth, Texas; [2]Department of Pharmacy, Children's Hospital of The King's Daughters, Norfolk, Virginia; Departments of [3]Pharmacy and [4]Pediatric Gastroenterology and Nutrition, Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio

This study compared the safety and efficacy of enterally administered pantoprazole, omeprazole and ranitidine at raising gastric pH above 4 in children with gastroesophageal reflux disease. Children with gastrostomy tubes that were being treated with one of the three drugs were included. Caregivers were taught to measure gastric pH. Dose, time of last meal, time of last dose, and time of gastric pH were collected. Four weekly pH measurements were compared among the groups. Seventeen patients were enrolled. Six received ranitidine, 6 received omeprazole, and 5 received pantoprazole. Mean doses were: ranitidine 6.8 mg/kg/day, omeprazole 1.4 mg/kg/day and pantoprazole 1.3 mg/kg/day. Mean gastric pH was 3, 4.3, and 4 for the ranitidine, omeprazole and pantoprazole groups, respectively. Twenty-nine percent of pH readings in the ranitidine, 66% in the omeprazole, and 60% in the pantoprazole group were above 4. Comparing pH to time since last dose, ranitidine failed to routinely achieve pH > 4. Pantoprazole and omeprazole achieved this, but by 12 hours after the dose both failed to maintain pH > 4. Pantoprazole and omeprazole appear more effective at controlling gastric pH than ranitidine. Pantoprazole appears safe, however doses of 1–1.5 mg/kg/day once daily may not be effective in maintaining gastric pH > 4 in children with GERD.

KEYWORDS: omeprazole, pantoprazole, pediatrics, ranitidine, reflux

J Pediatr Pharmacol Ther 2004;9:198-201

INTRODUCTION

Gastroesophageal reflux disease (GERD) is associated with significant morbidity and results in significant health care expenditure each year.[1] GERD is a normal physiologic process in infants, especially premature infants, that generally resolves by 12 months of age.[2] However, children with GERD can have complications such as failure to thrive, chest pain, bronchospasm and apnea. The overall estimated incidence of GERD is 18% in children, which increases up to 70% in patients with comorbidities.[3] GERD accounts for numerous physician office visits, emergency room visits, and hospital admissions every year. There are many non-pharmacological and pharmacological treatment options available for the treatment of GERD, but few have been studied in pediatric patients. Proton pump inhibitors (PPI's) have been the mainstay of GERD treatment in adults since the introduction of omeprazole in 1989.[4] Pantoprazole is one of the newest PPI's that has been approved by FDA for the short-term treatment of erosive esophagitis associated with GERD and long-term treatment of pathological hypersecretory conditions in adults.[5] Additionally, many hospitals are adding pantoprazole to their

ABBREVIATIONS: GERD, Gastroesophageal reflux disease; PPI, proton pump inhibitor

Address reprint requests to: Claire E. Cuttica, PharmD, Cook Children's Medical Center, 801 Seventh Avenue, Fort Worth, TX 76104, e-mail: clairec@cookchildrens.org

Table 1. Patient demographics

	RANITIDINE	OMEPRAZOLE	PANTOPRAZOLE
Weight (kg) mean [range]	25.3 [8.5–78.8]	18.4 [11.1–35.4]	12.7 [4.7–24.1]
Age (years) mean [range]	6.1 [1.6–14.6]	5.4 [1.75–13.9]	3.8 [0.5–10.8]
Male (%)	50	50	60
Caucasian (%)	50	100	100
Dose (mg/kg/d) mean [range]	6.8 [2.1–9.6]	1.4 [0.6–1.8]	1.3 [1–2]

formularies since it is available intravenously. Currently there are no large randomized double-blind trials designed to evaluate the safety and efficacy of pantoprazole in children. The purpose of this prospective pilot study was to compare the ability of pantoprazole, omeprazole and ranitidine to safely maintain gastric pH > 4 in pediatric patients with GERD.

METHODS

This prospective, three-arm, parallel group study was approved by the Institutional Review Board at the Cincinnati Children's Hospital Medical Center. All patients from the aerodigestive clinic, the rehabilitation clinic, and the hospitalized population at Cincinnati Children's Hospital Medical Center were eligible for inclusion provided they had a gastrostomy tube in place and were being treated with one of the three study medications. Initiation of therapy was based on clinical need and was not instituted in any patient for study purposes. Likewise, dosages were not adjusted based on the results of this study. While commercially available ranitidine syrup (15 mg/mL) was used, the omeprazole (2 mg/mL) and pantoprazole (2 mg/mL) suspensions were extemporaneously compounded by the pharmacy according to previously published procedures.[6,7] Exclusion criteria included: 1) age older than 18 years of age; 2) those receiving 24-hour continuous tube feeds; 3) renal dysfunction (i.e., serum creatinine > 2 times the upper limit of age-related normal values); 4) hepatic dysfunction (defined as aspartate transaminase > 2 times the upper limit of age-related normal values); or 5) concomitant treatment with a bismuth-containing preparation or sucralfate. Written informed consent was obtained from all parents or legal guardians, or from the patient when appropriate. Data collected for population characteristics included age, race, weight, diagnosis, and drug therapy. Caregivers were educated on the proper method of obtaining a gastric aspirate and the procedure to measure the gastric pH. Gastric aspirates were collected through the gastrostomy tube and gastric pH was measured using Gastroccult (Beckman Coulter Inc. Fullerton, CA). The caregiver was instructed to take a pH reading prior to a scheduled dose on an empty stomach once a week for the four-week study period. Caregivers were called the day before the pH was scheduled to be measured, as a reminder, and were called the day after to obtain the results. The caregiver was also asked to record the time of the patient's last meal, the time of the last dose, the time the gastric pH was measured, and the gastric pH reading. A gastric pH reading > 4 was considered effective for the treatment of GERD. All data is presented as mean ± SD.

RESULTS

Seventeen patients were enrolled in this study between October 2002 and May 2003. Six patients were enrolled in the ranitidine group, 6 in the omeprazole group, and 5 in the pantoprazole group. Thirty-five percent (n = 6) of the patients had a primary diagnosis of cerebral palsy and/or seizure disorder, 18% (n = 3) had bronchopulmonary dysplasia, 18% (n = 3) had infantile spasms, and 12% (n = 2) had DiGeorge Syndrome. All patients in this study had GERD as a secondary diagnosis. Table 1 summarizes the other pertinent patient characteristics. The mean gastric pH was 3 ± 1.5 for the ranitidine group, 4.3 ± 2.3 for the omeprazole group, and 4 ± 1.7 for those receiving pantoprazole. Only 29% of the gastric pH values measured in the ranitidine group were > 4 compared to 66% in the

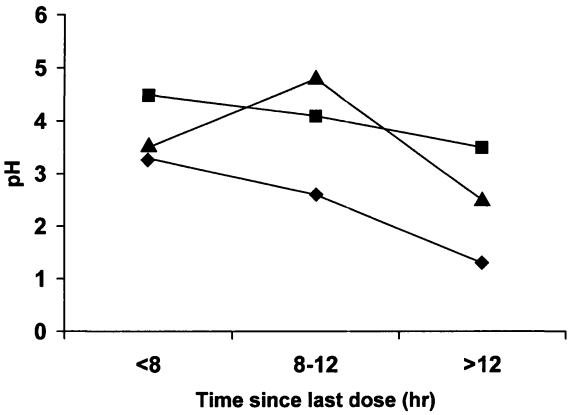

Figure 1. Gastric pH following last administered dose of acid suppressant. -◆- Ranitidine; -■- Omeprazole; -▲-Pantoprazole.

omeprazole group and 60% in the pantoprazole group. Figure 1 compares the gastric pH to the time since administration of the last dose of medication. Eight hours after the administration of ranitidine, the mean pH in that group was 3.3 ± 1.2. This compares to a mean pH of 4.5 ± 0.6 in the omeprazole group and 3.5 ± 1.0 in the pantoprazole group at the same time point. The mean pH 8–12 hours after the last dose was 2.6 ± 0.6 for ranitidine versus 4.1 ± 1.6 for those receiving omeprazole and 4.8 ± 0.4 for the pantoprazole group. Greater than 12 hours since the last dose of medication, the mean pH for all three groups was below the minimum target pH. Because of the array of dosing intervals prescribed for these three medications, a relationship between the dosing interval and the mean gastric pH was analyzed. Once-daily omeprazole produced a mean pH of 5, while pantoprazole given once daily resulted in a mean pH of 3.5 ± 1.4. No patient received ranitidine once daily. Mean gastric pH in patients treated twice daily with ranitidine was 2.6 ± 1.7, 4.0 ± 1.6 for those prescribed omeprazole, and 4.3 ± 0.8 for those receiving pantoprazole. Ranitidine was the only medication given three times a day. Treatment failure was noted in three of the ranitidine-treated patients. All three were unable to achieve a gastric pH in the target range and continued to have clinical symptoms associated with GERD. There were no differences in reported adverse effects among the three medications.

DISCUSSION

This study is in agreement with the adult literature that demonstrates PPI's are more effective than histamine 2 receptor antagonists in maintaining gastric pH in the target range for the treatment of GERD. The only treatment failures were in the ranitidine group. Three patients in that group consistently had low gastric pH measurements and had continued GERD symptoms. All of these patients were referred to their primary care doctors, and were subsequently changed to a PPI. The small sample size of this study made it difficult to determine significant differences between the two PPI's. While it may appear that omeprazole achieves a higher gastric pH, particularly when given once daily, it is important to point out that there were only four data points on the once daily omeprazole regimen. The pantoprazole data in that same analysis is based on twelve data points. Although statistical significance was not determined in this study, it appears that pantoprazole is at least similar in efficacy to omeprazole in pediatric patients.

Dosing recommendations for children with GERD also need to be established. While this pilot study demonstrates that pantoprazole is safe, it also raises the concern that an initial pantoprazole dose of 1–1.5 mg/kg/day given once daily may not be enough to maintain a gastric pH > 4 in children with GERD. Interestingly, the one point where this study appears to be in conflict with the published literature is in the relationship between the measured gastric pH and the dosing interval. Current dosing recommendations for pantoprazole in adults advocate once daily dosing. Our data indicates that children may benefit from at least two doses a day since the gastric pH consistently fell below 4 during the period greater than 12 hours after the last dose of pantoprazole. One reason for this difference might be higher metabolic capacity in children as compared to adults. Anderson et al. in a pharmacokinetic study of omeprazole demonstrated that children need higher doses of omeprazole on a per kilogram basis due to increased rate of drug metabolism.[8] This may also be the case with pantoprazole.

There are limitations to this pilot study. First, this study involved only a small, select group of pediatric patients. The efficacy results however are similar to those published for adults. Second, having the caregivers measure the gastric pH at home introduces variability in collection techniques and subjectivity in interpreting the gastric pH. Despite these limitations, there was a trend noted from these results between both of the PPI's and ranitidine.

CONCLUSION

It appears that both pantoprazole and omeprazole are more effective at controlling gastric pH than histamine 2 receptor antagonists in children with GERD. Pantoprazole appears to be safe, however an initial dose of 1–1.5 mg/kg/day given once daily may not be effective in maintaining the gastric pH > 4 in children with GERD.

REFERENCES

1. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002;122:1500-11.
2. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 1997;151:569-72.
3. Zalzal GH, Tran LP. Update on the pediatric airway—Pediatric gastroesophageal reflux and laryngopharengeal reflux. Otolaryngol Clin North Am 2000;33:151-61.
4. Patel AS, Pohl JF, Easley DJ. Proton pump inhibitors and pediatrics. Pediatr Rev 2003;24:12-6.
5. Poole P. Pantoprazole. Am J Health-Syst Pharm 2001;58: 999-1008.
6. Dentinger PJ, Swenson CF, Anaizi NH. Stability of pantoprazole in an extemporaneously compounded oral liquid. Am J Health-Syst Pharm 2002; 59:953-6.
7. Quercia RA, Fan C, Liu X, Chow MS. Stability of omeprazole in an extemporaneously prepared oral liquid. Am J Health-Syst Pharm 1997;54:1833-6.
8. Madrazo-de la Garza A, Dibildox M, Vargas A, Delgado J, Gonzalez J, Yanez P. Efficacy and safety of oral pantoprazole 20 mg given once daily for reflux esophagitis in children. J Pediatr Gastroenterol Nutr 2003;36:261-5.
9. Anderson T, Hassall E, Lundborg P, Shepherd R, Radke M, Marcon M, et al. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. Am J Gastroenterol 2000;95: 3101-6.