A Randomized Clinical Trial Comparing the Efficacy of Ranitidine and Famotidine on Intragastric Acidity in Critically Ill Pediatric Patients

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Abstract

We examined the efficacy of intravenous ranitidine and famotidine on raising intragastric *p*H in each of 10 critically ill pediatric patients. The severity of illness was assessed by using the modified zinner index score. The study had 3 phases and each phase took 24 hours. Intragastric *p*H was measured by continuous *p*H monitoring digitrapper for 72 hours. In phase 1 and 3, the patients did not receive any H_2 blockers. In phase 2, they were randomized to receive intravenous ranitidine or famotidine. The majority of cases had intragastric *p*H < 4 in day 1 (base line). Ranitidine and famotidine increased total time of intragastric *p*H ≥ 4 from the base line during day 2, 38.2 ± 16.9 per cent and 60.3 ± 24.8 per cent respectively (P0.004), but there was no statistical difference between the 2 medications in both Zinner index score 1 and score greater than 1 group (P 0.08, 0.45). Three cases in the famotidine group had successful prophylaxis with total time *p*H ≥ 4 more than 80 per cent. Famotidine appeared to have a trend toward increasing intragastric *p*H in critically ill pediatric patients.

Between 3 and 25 per cent of critically ill adult patients have gastrointestinal hemorrhage due to acute gastroduodenal mucosal injury[1,2]. The etiology of injury is still unknown but there are numerous related factors such as ischemia, increased acid and pepsin secretion and decreased mucous bicarbonate barrier and prostaglandin synthesis[3,4]. When gastric *p*H is about 4, mucosal damage does not occur. Little data exist in the pediatric literature about prophylaxis of acute gastric mucosal damage. The medications usually used to prevent gastrointestinal hemorrhage in critically ill children are antacid, H_2 blocker and sucralfate. Cid JL et al used ranitidine in prophylaxis of acute gastric mucosal damage in children and found that a dose of 1.5 mg per kg per dose every 6 hours was effective in raising the gastric *p*H above 4[5]. Treem WR et al used famotidine in

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a dose of 0.4 mg per kg per dose every 8 hours which also had good efficacy[6]. The objective of this study was to compare the efficacy of ranitidine with famotidine on intragastric acidity in critically ill pediatric patients.

PATIENTS AND METHOD

This study was approved by the ethics committe, Siriraj Hospital, School of Medicine, Mahidol University. The patients were aged from 2 months to 12 years. The severity of illness was assessed by using the modified Zinner index score[5]. All patients were given one point for each of the following risk factors:1) respiratory insufficiency (mechanical ventilation or continuous positive airway pressure); 2) shock; 3) cardiac insufficiency; 4 neurological disturbance (coma, convulsion); 5) sepsis; 6) metabolic acidosis with *p*H < 7.25 ; 7) steroid administration (dose of > 2 mg per kg of methylprednisolone). Because both medications are metabolized by the liver and excreted *via* the kidneys, we didn't include hepatic dysfunction and renal insufficiency in the modifed Zinner index score. In addition, coagulopathy and thrombocytopenia were not included due to increasing the risk of gastrointestinal bleeding. The patients did not have a history of active peptic acid disease, GI bleeding or receiving H_2 blockers, antacid or sucralfate within 24 hours prior to the study.

The study had 3 phases and each phase took 24 hours. It was started on the first day of admission in the pediatrics ICU. All patients were not fed during the study and underwent continuous intragastric *p*H monitoring by using digitrapper model MK III (Synnectic, U.S.A.) for 72 hours. The glass *p*H probe was calibrated with a buffer solution of *p*H 1 and 7 and had its tip placed at the gastric fundus. A nasogastric tube was inserted in the stomach and gastric contents were aspirated every 4 hours during the study to detect upper gastrointestinal hemorrhage. The intensity of macroscopic hemorrhage was classified into 3 categories : non hemorrhage, slight (coffee ground or small amount of red blood) and important (with hematologic and or hemodyamic repercussion)[7]. Serum creatinine, aminotransferase, and coagulogram were monitored daily. In phase 1 and 3, the patients did not receive any H_2 blockers. In phase 2, they were randomized to receive intravenous rantidine (1.5 mg per kg per dose every 6 hours) or famotidine (0.4 mg per kg per dose every 8 hours). H_2 blocker prophylaxis was considered successful when gastric *p*H is $\geq$4 for more than 80 per cent of the study time for each patient.

Statistics. A comparative analysis of acid secretion inhibition between the 2 medications was analysed by the U-Mann Whitney test. The comparing efficacy of the 2 medications in each Zinner index score 1 and > 1 was analysed by 2 factors ANOVA.

RESULT

Twenty patients were studied with ten cases in each group. Twelve boys and 8 girls aged from 2 months to 12 years (median 6 months). The

Table 1. The diagnoses and number of patients in each group.

	Ranitidine	Famotidine	Total
Number (M/F)	5 / 5	7 / 3	12 / 8
Index score			
1	7	5	12
2	3	4	7
3		1	1
Diagnosis			
CHD with pneumonia	5	4	9
Pneumonia	4	1	5
Pneumonia with sepsis	-	2	2
Chickenpox with pneumonia	1	-	1
Hypotonia with pneumonia	-	1	1
Meningitis with coma	-	1	1
Near drowning with coma	-	1	1

diagnoses of the patients were : 9 congenital heart disease with pneumonia, 5 pneumonia, 2 pneumonia with sepsis and 4 others. The diagnoses and number of patients in each group of modified Zinner index score are presented in Table 1. There were episodes of slight hemorrhage in 2 and 1 patients in the ranitidine and famotidine group respectively.

Group 1 (ranitidine). The majority of cases had *p*H below 4 during day 1 except 2 cases having a total time *p*H $\geq$ 4 8.6 per cent and 4.2 per cent. The total time *p*H $\geq$ 4 on day 2 (mean $\pm$ SD) was 39.5$\pm$15.8 per cent. After stopping the ranitidine, there was only one case having *p*H $\geq$ 4 (3.7%) (Fig. 1.A).

Group 2 (famotidine). Four cases had gastric *p*H $\geq$ 4 on day 1 (2.4%, 3.5%, 4.7%, 7%). The total time *p*H $\geq$ 4 on day 2 (mean $\pm$ SD) was 62.2 $\pm$ 24.5 per cent and 3 cases had *p*H $\geq$ 4 on day 3 (24%, 11.3%, 11.4%) (Fig. 1.B).

The total time of gastric *p*H $\geq$ 4 during day 2 increased from the baseline on day 1 which was 38.2 $\pm$ 16.9 per cent (group1) and 60.3$\pm$24.8 per cent (group 2) which showed significant statistical difference (p 0.04). However, there was no difference when we compared both Zinner index score 1 and > 1 groups (p 0.08 and 0.45) (Table 2). Three cases in the famotidine group had total time *p*H $\geq$ 4 more than 80 per cent (85.5%, 88%, 100%). The study showed no statistically significant correlation

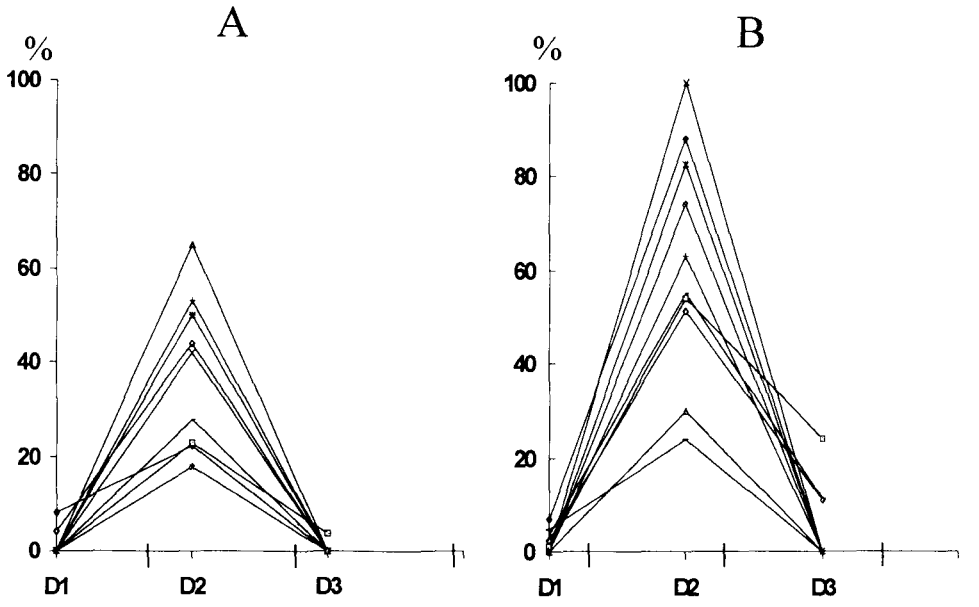

Fig. 1. Percentage of total time with *p*H $\geq$ 4 in each 24 hour period of ranitidine (A) and famotidine (B) group.

Table 2. Total time *p*H $\geq$ 4 increased from base line during day 2 in each group.

Patients	Ranitidine	Famotidine	P
Total	38.2 $\pm$ 16.9 %	60.3 $\pm$ 24.8 %	0.04
Score 1 group	36.2 $\pm$ 13.5 %	61.6 $\pm$ 29.7	0.08
Score > 1 group	42.9 $\pm$ 26.3 %	59.1 $\pm$ 22.4	0.45

between modified Zinner index score and efficacy of the 2 medications.

DISCUSSION

The majority of our patients were aged below 1 year and the most common underlying illness was congenital heart disease with pneumonia. Because liver failure, renal failure and abnormal coagulogram were excluded, the majority of cases admitted to the pediatric ICU were not involved. The patients had a moderate risk (Zinner index score 1 or 2) of developing upper gastrointestinal hemorrhage. Only 3 cases (15%) had slight hemorrhage which resolved without any additional therapy.

Lacroix J et al found that the occurrence rate of important upper gastrointestinal hemorrhage in pediatric patients was 38 per cent[8], but Lopez-Herce J et al reported 20 per cent[7]. In addition, they suggested that a Zinner index score of 5 or more predicted important upper gastrointestinal hemorrhage with sensitivity of 71.9 per cent and specificity of 85.8 per cent. All patients with hemorrhage had a score of ≥ 3 (renal failure, sepsis, liver failure, heart failure, gluocorticoid administration and metobolic acidosis). Respiratory insufficiency and neurological alteration appeared not to be more frequent in children with hemorrhage; therefore, our patients had a low risk of developing important hemorrhage.

There were different data on intragastric *p*H in adult and pediatric ICU patients. Moore JG et al revealed that adult patients had normosecretory group 66 per cent and hyposecretory group 34 per cent in the first 24 hours of study[9]. Geus WP et al reported that intragastric *p*H ≥ 4 was 74 per cent of time during day 1, 34 per cent during day 2 and 16 per cent during day 3 in postoperative adult patients[10]. Lopez-Herce J et al found that thirty per cent of patients had an initial gastric ≥ 4 but the majority of critically ill pediatric patients maintained acid gastric *p*H during the illness[7]. Our study showed 6 patients having gastric *p*H ≥ 4 with a maximum total time only 8.6 per cent in day 1. Intragastric acidity occurring initially or during the illness will play a role in the pathogenesis of acute gastric mucosal damage, therefore, prophylaxis with H_2 blooker or sucralfate is usually recommended to reduce the occurrence rate of important gastrointestinal hemorrhage.

Ranitidine was able to raise intragastric *p*H ≥ 4 with total time 39.5 ± 15.8 per cent in day 2, but there was no case having a total time of more than 80 per cent. This data is different from a previous study by Cid J L et al showing 8 of 10 pediatric patients with successful ranitidine prophylaxis. Famotidine had the advantage over previous H_2 blocker acids including a longer duration of action and more potent suppression of gastric secretion. This study showed total time *p*H ≥ 4 62.2 ± 24.5 per cent and 3 cases having successful prophylaxis in a famotidine group. Although there was no statistical difference in raising intragastric *p*H between the 2 medications in both Zinner index score 1 and >1 group, famotidine had a trend toward more potent action on gastric acid suppression.

ACKNOWLEDGEMENT

The authors wish to thank the Faculty of Medicine, Siriraj Hospital, Mahidol University for the research grant support and Mr. Suthipol Udompunthuruk for his assistance with the statistical analysis.

(Received for publication on February 14, 1997)

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การศึกษาเปรียบเทียบผลของยารานิติดีน และฟาโมติดีน ในการลดภาวะเป็นกรดในกระเพาะอาหารในผู้ป่วยเด็กที่เจ็บป่วยรุนแรง

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คณะผู้ศึกษาได้ทำการทดลองเปรียบเทียบผลของยา ranitidine และ famotidine ในการลดภาวะเป็นกรดในกระเพาะอาหารในผู้ป่วยเด็กที่เจ็บป่วยรุนแรงจำนวนกลุ่มละ 10 ราย การทดลองในผู้ป่วยแต่ละรายใช้เวลานาน 3 วัน โดยในช่วงวันแรกและวันที่สามผู้ป่วยไม่ได้ยา H_2 blocker แต่ในช่วงวันที่ 2 ได้รับยา famotidine หรือ ranitidine ฉีดเข้าเส้น ระดับพีเอชในกระเพาะอาหารถูกบันทึกโดยเครื่อง *p*H monitoring (Synnectic U.S.A.) ตลอดระยะเวลา 3 วัน ระยะเวลาภายใน 24 ชั่วโมงที่ค่าพีเอช ในกระเพาะอาหาร $\geq$ 4 ถูกแสดงเป็นค่าเปอร์เซ็นต์โดยระยะเวลา 24 ชั่วโมงถือเป็น 100% ระดับพีเอช ในกระเพาะอาหารในวันที่ 1 ของผู้ป่วยทั้ง 2 กลุ่มส่วนใหญ่จะมีค่าน้อยกว่า 4 ในวันที่ 2 กลุ่มผู้ป่วยที่ได้รับยา famotidine สามารถเพิ่มระยะเวลาที่ทำให้พีเอช $\geq$ 4 จากค่าในวันที่ 1 60.3 $\pm$ 24.8 % ซึ่งมากกว่า กลุ่มที่ได้รับยา ranitidine ซึ่งมีค่าเพิ่มขึ้น 38.2 $\pm$ 16.9% (P0.004) แต่ถ้าเปรียบเทียบผลของยาแต่ละตัวในกลุ่มผู้ป่วยที่แบ่งตามคะแนนแสดงความรุนแรง (Zinner index score 1 และมากกว่า 1) พบว่าไม่มีความแตกต่างกันทางสถิติ (P0.08, 0.45) ผู้ป่วย 3 รายในกลุ่ม famotidine สามารถทำให้ระยะเวลาในวันที่ 2. ที่ พีเอช $\geq$ 4 มากกว่า 80% ยา famotidine มีแนวโน้มที่จะออกฤทธิ์ได้ดีในการลดภาวะเป็นกรดในกระเพาะอาหารในผู้ป่วยเด็กที่เจ็บป่วยรุนแรง

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