Intravenous bolus versus continuous infusion of famotidine or ranitidine on 24 h intragastric acidity in fasting healthy volunteers

ABR THOMSON MD PHD FRCPC FACP FRS FACC, P KIRDEIKIS RN, D WASARAB-ROLLAND,
L ZUK RN, B PINCHBECK PHD

ABR THOMSON, P KIRDEIKIS, D WASARAB-ROLLAND, L ZUK, B PINCHBECK. Intravenous bolus versus continuous infusion of famotidine or ranitidine on 24 h intragastric acidity in fasting healthy volunteers. *Can J Gastroenterol* 1995;9(1):47-50. Infusions of H₂-receptor antagonists may be clinically indicated to maintain intragastric pH above 4 to reduce acute gastric mucosal lesions or to treat patients with bleeding peptic ulcers. Eight fasting healthy volunteers were randomly assigned to receive ranitidine infusion alone (150 mg/day), ranitidine infusion plus 50 mg bolus injection of ranitidine (total of 200 mg/day), famotidine infusion alone (40 mg/day) or famotidine infusion plus 40 mg bolus injection of famotidine (total of 80 mg/day). Gastric fluid contents were aspirated for 24 h and collected as half-hourly samples in which pH measurements were made. Measures analyzed were mean and median pH, percentage pH at or below 3, 4 or 5 for the 24 h period, daytime, evening and nighttime. The data for each of the variables were analyzed as a Latin square crossover design of variance therapy; base pH before treatment administration in each crossover phase was employed as the covariant. Significant differential treatment means were tested by Newman-Keul's multiple range test at the 5% level of significance. The mean and median evening pH were higher after famotidine than after ranitidine infusion, but all other pH readings were similar when using these doses. The addition of an initial loading bolus of 50 mg ranitidine to the ranitidine infusion did not result in any added differences in pH, whereas the addition of an initial loading bolus of 40 mg famotidine to the famotidine infusion resulted in a higher 24 h median pH, as well as a lower percentage of pH values of 4 or below, 16.6% versus 28.5%, $P < 0.05$. However, the loading doses of ranitidine and famotidine were not equivalent in potency, and studies are needed to compare the potency of equivalent doses of ranitidine and famotidine when given by bolus plus infusion. Also the clinical relevance of these findings needs to be explored further in the type of individuals potentially requiring intravenous H₂-receptor antagonists. (*Pour résumé, voir page 48*)

Key Words: Acid suppression, H₂-receptor antagonists

Nutrition and Metabolism Research Group, Department of Medicine, Division of Gastroenterology and Clinical Investigation Unit, University of Alberta, Walter Mackenzie Health Sciences Centre, Edmonton, Alberta

Correspondence and reprints: Dr ABR Thomson, 519 Robert Newton Research Building, University of Alberta, Edmonton, Alberta T6C 2C2. Telephone (403) 492-6490, Fax (403) 492-7964

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REDUCTION OF INTRAGASTRIC acidity with intravenous H₂-receptor antagonists has been used for the prevention of stress-related gastric mucosal injury in intensive care unit patients and for the prevention and treatment of upper gastrointestinal bleeding. It is generally thought that intragastric acidity has to be continuously reduced to a level corresponding to an intragastric pH of 4 or greater (1-3). The use of continuous infusion of H₂-receptor antagonists in critically ill patients has been reviewed (4). Intravenous cimetidine controls pH over a 24 h period when given in a dose of 900 mg/day (37.5 mg/h) (5,6). Ostro and co-workers (7) have suggested that continuous infusion of cimetidine at 37.5 mg/h after a loading dose of 300 mg is superior to repeated 300 mg boluses every 6 h. Ranitidine injections of 150 mg/day or 6.25 mg/h leads to a 24 h median intragastric pH of 6.3 in duodenal ulcer patients (8). No loading dose of ranitidine is needed for rapid onset (9,10). Siepler and colleagues (4) reported comparable effects on intragastric pH of continuous intravenous infusion of famotidine 1.7 mg/h (40 mg/day), ranitidine 8.3 mg/h (200 mg/day) and cimetidine 50 mg/h (1200 mg/day). Hannon et al (5) used an automatic computerized pump to maintain a constant intragastric pH above 6.0, and demonstrated that

Bolus intraveineux versus perfusion continue de famotidine ou de ranitidine et acidité intragastrique sur 24 heures chez des volontaires sains à jeun

RÉSUMÉ : Des perfusions d'anti-H₂ peuvent être cliniquement indiquées afin de maintenir un pH intragastrique supérieur à 4 et atténuer ainsi les lésions aiguës de la muqueuse gastrique ou pour traiter les patients qui souffrent d'ulcères gastro-duodénaux hémorragiques. Huit volontaires sains à jeun ont été assignés au hasard à une perfusion de ranitidine seule (150 mg/jour), une perfusion de ranitidine plus injection en bolus de 50 mg de ranitidine (pour un total de 200 mg/jour), une perfusion de famotidine seule (40 mg/jour) ou une perfusion de famotidine plus injection en bolus de 40 mg de famotidine (pour un total de 80 mg/jour). Le liquide gastrique a été aspiré au cours d'une période de 24 heures et recueilli sous forme d'échantillons aux demi-heures sur lesquels des mesures du pH ont été faites. Les mesures analysées étaient le pH moyen et médian, le pourcentage des pH égaux ou inférieurs à 3, 4 ou 5 au cours de la période de 24 heures, durant le jour, le soir et la nuit. Les données pour chacune des variables ont été analysées selon un modèle croisé en carré latin. Le pH de départ, avant l'administration du traitement, dans chaque phase croisée a été employé comme covariable. Les moyennes différentielles significatives des traitements ont été testées au moyen de l'épreuve à variables multiples de Newman-Keul, avec un degré de portée de 5 %. La moyenne et la médiane du pH du soir ont été plus élevées après la perfusion de famotidine qu'après la perfusion de ranitidine, mais toutes les autres lectures de pH étaient semblables avec ces doses. L'ajout d'un bolus de charge initial de 50 mg de ranitidine à la perfusion de ranitidine n'a pas provoqué de différence de pH, alors que l'ajout d'un bolus de charge initial de 40 mg de famotidine à la perfusion de famotidine a donné lieu à une médiane du pH sur 24 heures plus élevée, de même qu'à un pourcentage plus faible des valeurs de pH de 4 ou moins, 16,6 % contre 28,5 %, $P < 0,05$. Toutefois, les doses de charge de ranitidine et de famotidine n'étaient pas équivalentes en terme de puissance. D'autres études sont nécessaires en vue de comparer la puissance de doses équivalentes de ranitidine et de famotidine lorsqu'elles sont administrées en bolus et en perfusion. La pertinence clinique de ces analyses doit encore être étudiée chez les sujets qui pourraient nécessiter l'administration d'anti-H₂ par voie intraveineuse.

mean famotidine use in normal volunteers was greater with a 12 h bolus followed by infusion compared with infusion of famotidine alone, and surprisingly onset of action was not apparently faster. The efficacy of continuous infusion versus bolus injection followed by continuous infusions was not determined. The purpose of this study was to test the hypothesis that famotidine and ranitidine given by an initial bolus followed by a continuous infusion of drug is superior to initial infusion alone to maintain intragastric acidity above pH 4.0.

VOLUNTEERS AND METHODS

Eight healthy volunteers, four females and four males, ranging in age from 22 to 36 years (mean 28.5) were recruited for the study. They were

healthy at the pretreatment evaluation and gave written informed consent to participate in the study. The exclusion criteria included pregnancy, planned pregnancy or lactation; active ulceration and/or peptic ulcer symptoms that required continuous medical treatment; treatment with antiseecretory drugs or regular antacid treatment during the week preceding the study start; pyloric stenosis; history of gastric surgery, excluding simple closure or a perforation; chronic alcoholism, drug abuse or other conditions associated with poor volunteer compliance; cardiovascular disease or other conditions that might have compromised the volunteer's tolerance to parenteral fluid loading; and any other significant disease that might have placed the volun-

teer at risk or interfere with the study procedures.

The study was conducted according to the 'Declaration of Helsinki' as revised in Tokyo, Japan, 1975. Review and approval of the study by the institutional review committee of the University of Alberta was obtained before the start of the study. Before entry into the study each volunteer underwent a clinical examination including medical history, physical examination and a laboratory screen. Blood and urine samples for a laboratory screen were taken at the pre-entry examination and follow-up. The variables measured included hemoglobin concentration, red blood cell, white blood cell and platelet count, aspartate aminotransferase, glutamic pyruvic transaminase, alkaline phosphatase, sodium, potassium, calcium, creatinine, total bilirubin, and glucose and albumin concentrations.

The volunteers refrained from excessive alcohol consumption during the study. The volunteers took no alcohol for the day before each 24 h acidity test. Before each experiment day the volunteers were instructed to have the main evening meal no later than 20:00 and, if desired, a light evening snack no later than 22:00, after which fasting took place. No antacids were allowed from 08:00 on the day before study.

Study design: Each of the eight volunteers took part in four 24 h experiments, separated by at least seven days. In each experiment ranitidine or famotidine was given in random order by intravenous bolus plus infusion, or by infusion without bolus.

For the primed or 'bolus' infusions, 50 mg of ranitidine or 40 mg of famotidine, in 2 mL, was mixed with 98 mL of 2/3+1/3 glucose/saline intravenous solution. Each dose was given over 10 mins (600 mL/h) at 08:00 only. After an initial dose of ranitidine 50 mg or famotidine 40 mg, the drug was administered by continuous infusion using an IVAC 570 pump at a rate of 6.25 mg/h ranitidine (ie, 150 mg/day) or 1.7 mg/h famotidine (ie, 40 mg/day), in 2/3+1/3 given intravenously at a rate of 100 mL/h. For the nonprimed infusions, the infusion of famotidine or ranitidine was similar to the primed infusion, but was

TABLE 1
Effect of intravenous H₂-receptor on measures of intragastric pH

	Treatment groups			
	Ranitidine infusion	Famotidine infusion	Ranitidine infusion + bolus	Famotidine infusion + bolus
24 h mean pH	4.69±1.06 _b	5.29±1.40 _{ab}	5.02±1.13 _b	5.96±9.97 _a
Day mean pH	5.42±1.25 _a	5.59±1.37 _a	5.59±1.09 _a	6.63±0.83 _a
Evening mean pH	3.75±0.076 _c	5.21±1.61 _{ab}	4.29±1.31 _{bc}	5.41±1.43 _a
Night mean pH	4.51±1.69 _b	5.42±1.74 _{ab}	4.72±1.58 _b	5.63±1.49 _a
24 h median pH	4.67±1.61 _b	5.38±1.65 _b	5.46±1.52 _b	6.45±0.82 _a
Day median pH	5.81±1.38 _a	5.64±1.58 _a	5.88±1.43 _a	6.76±0.42 _a
Evening median pH	3.21±0.96 _c	5.18±1.89 _{ab}	4.24±1.84 _{bc}	5.64±1.72 _a
Night median pH	4.54±1.86 _b	5.48±1.94 _{ab}	5.13±1.93 _{ab}	5.92±1.58 _a
24 h percentage pH <4.0	0.418±0.261 _b	0.285±0.270 _b	0.323±0.221 _b	0.166±0.155 _a
Day percentage pH <4.0	0.280±0.253 _a	0.291±0.259 _a	0.211±0.170 _a	0.106±0.126 _a
Evening percentage pH <4.0	0.645±0.230 _a	0.348±0.388 _b	0.466±0.294 _{ab}	0.246±0.279 _b
Night percentage pH <4.0	0.474±0.426 _a	0.266±0.399 _a	0.406±0.338 _a	0.205±0.259 _a

*Means within the same column and followed by the same letter are not significantly different. Times are designated as day (08:00-20:00), evening (20:00-24:00) and night (24:00-08:00)

not preceded by a bolus injection of ranitidine or famotidine. The total daily doses were: ranitidine infusion, 150 mg/day; ranitidine bolus plus infusion, 200 mg/day; famotidine infusion, 40 mg/day; famotidine bolus plus infusion, 80 mg/day.

Twenty-four hour intragastric acidity: In the morning of each experiment day, having fasted overnight, the volunteer came to the clinical investigation unit. An indwelling cannula was inserted in a forearm vein for infusion of famotidine or ranitidine. A 12 or 14 F nasogastric tube was passed and positioned in the most distal part of the stomach. The position was checked by the water recovery technique; 5 mL samples of gastric juice were aspirated 5 mins before the beginning of the study, half-hourly between 00:00-14:00 and hourly between 14:00-24:00. The subjects' fluid load was maintained by hourly recording of input/output and regular blood pressure measurement. During the experiment no food was allowed. The volunteers were allowed to rinse their mouths with tap water, but were instructed not to swallow any. A 2/3+1/3 glucose/normal saline solution (100 mL/h) was given as an intravenous drip to maintain patient hydration. The volunteers were monitored for signs of possible adverse effects from the par-enteral fluid load. The following specific safety assessments were done: blood pressure at 6 h intervals; and ac-

curate fluid intake and output recordings through the 24 h experiment. In each gastric sample pH was recorded to the nearest 0.01 unit, using a combined glass and reference electrode and a pH meter (Corning 3AG 500 M/A). The electrode was calibrated with standard buffer solutions of pH 2.01, 4.03 and 7.00. The calibration was checked at the beginning and at the end of the 24 h test. During the 24 h experiment the volunteers were encouraged to stay in bed. The volunteers stayed in the laboratory until about 09:00.

Statistical design: The study design is a Latin square crossover with multiple measurements at each phase of the crossover. Each of the eight healthy volunteers was randomly assigned to the treatment sequence, and the order of the treatments in each sequence was dictated by the Latin square. The measures analyzed were mean and median pH, and percentage pH less than 3.0, 4.0 or 5.0 for each of: the 24 h day, and the day (08:00-20:00), evening (20:00-24:00) and night (24:00-08:00) periods.

The data for each of the variables were analyzed as a Latin square crossover design analysis of covariance. The base pH, before treatment administration in each crossover phase, was employed as the covariate. An unrotated principle components analysis was also applied to the analysis variables to determine whether an underlying struc-

ture could be found for the variables. Significant differences among treatment means were tested by Newman-Keul's multiple range test at the 5% level of significance.

The treatment means for base pH were not found to be significantly different. For most measures, significant differences for the healthy volunteers were found, indicating that eight persons formed a minimum sample. Significant differences among treatments were found for 24 h, evening and night median pH; for evening percentage pH less than 3, and for 24 h and evening percentage pH less than 4.0. The effects due to the Latin square design were not significant for any of the variables. With the exception of evening mean pH, the covariate effects were also nonsignificant. The principle components analysis revealed that there were two primary components within the data. The first component was highly correlated with the 24 h measures and the mean pH measures for all periods for these data. The variables of the evening period are also of importance, as was earlier indicated in the analysis of covariance. The second component suggests that there is a residual factor which weakly correlates the variables of the day and night periods and which is not being estimated by the first component.

RESULTS

Famotidine infusion was superior to ranitidine infusion in terms of higher evening mean pH (5.21 versus 3.75), and higher evening median pH (5.18 versus 3.21) and lower evening percentage pH (34.8% versus 64.5%) less than 4 (Table 1); famotidine infusion was also superior to ranitidine in achieving a lower percentage of pH less than 3 (21.0% versus 56.0%) or pH less than 5 (40.0% versus 75.0%). No difference in any parameter was detected between ranitidine infusion alone and ranitidine infusion plus bolus (Table 1). In contrast, the addition of a bolus of famotidine to famotidine infusion, compared with famotidine infusion alone, resulted in a higher 24 h median pH (6.45 versus 5.38) and a lower 24 h percentage of pH values less than 4 (16.6% versus 28.5%, famotidine infusion plus bolus versus famotidine infusion alone, respectively).

DISCUSSION

The first clinical situation in which an intravenous H₂-receptor antagonist might be given is the intensive care unit, where it was elected to maintain the intragastric pH equal to or greater than four. A number of therapeutic regimens has been developed to enhance the acid inhibitory effect of H₂-receptor antagonists, and there is evidence that infusion therapy is superior to bolus therapy with cimetidine (7), but a loading dose of ranitidine does not add to the effect of intravenous infusion alone (8,9). In this study there was no added benefit achieved by the addition of a bolus of ranitidine before initiating a ranitidine infusion (Table 1). In contrast, giving a bolus of famotidine before a famotidine infusion resulted in higher ($P < 0.05$) 24 h median pH value, and a lower ($P < 0.05$) number of 24 h percentage of pH values less than 4 (16.6% versus 28.5%, famotidine infusion plus bolus versus famotidine infusion alone, respectively). The loading dose of famotidine, 40 mg, is not of equivalent potency to the 50 mg loading dose of ranitidine, so that it is not appropriate to compare the acid

inhibitory effect of this loading dose of ranitidine plus infusion versus famotidine bolus plus infusion. It is possible that a higher dose of ranitidine, like this higher dose of famotidine, might have an enhancing effect.

Intravenous H₂-receptor antagonists may be administered in the clinical setting where patients have peptic ulcer disease but are not able to take medication by mouth. The healing of duodenal ulcer has been shown to be a function of the number of hours per day when the intragastric pH is maintained at greater than 3 (10). Adding a bolus to the infusion of ranitidine did not give any added benefit to the percentage of pH values less than 3 (data not shown).

The cost of infusion therapy varies widely from institution to institution. At the Walter Mackenzie Health Science Centre in Edmonton, the 1993 daily cost of these treatments per patient day was: ranitidine infusion, \$7.56; famotidine infusion, \$7.48; ranitidine infusion plus bolus, \$10.04, and famotidine infusion plus bolus (at this dose), \$14.96. The acid inhibitory effect of ranitidine infusion was comparable with famotidine infusion, at almost equal cost. Greater acid inhibition could be achieved by adding famotidine bolus plus infusion, compared with famotidine infused alone (for example, 16.6% versus 28.5% of 24 h pH less than 4), but at approximately double the cost. Thus, using infused standard doses of famotidine resulted in lower evening values of mean and median pH, as well as a lower percentage pH values less than 4, with no added cost. Higher values of acid inhibition can be achieved using a loading dose of famotidine followed by famotidine infusion, but it is necessary to determine what is the ideal percentage of pH readings above a defined pH value (such as pH 4) required to prevent bleeding from stress ulceration, or to treat patients with bleeding peptic ulcers, before recommendations can be made about the optimal dose and therefore cost-effectiveness of H₂-receptor antagonist to be given intravenously. Fi-

nally, it should be stressed that these data obtained with healthy volunteers cannot necessarily be extrapolated to patients in the intensive care unit setting or to persons with peptic disorders.

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REFERENCES

1. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled randomized trial in 100 critically ill patients. *N Engl J Med* 1978;298:1041-5.
2. Silen W. The prevention and management of stress ulcers. *Hosp Pract* 1980;15:93-100.
3. Peterson WL, Richardson CT. Intravenous cimetidine and two regimens of ranitidine to reduce fasting gastric acidity. *Ann Intern Med* 1986;104:505-7.
4. Siepler JK, Trudeau W, Petty DE. Use of continuous infusion of histamine₂-receptor antagonists in critically ill patients. *DICP* 1989;23:S40-3.
5. Hannon A, Chesner I, Merki HS, Mann S, Walt RP. Use of automatic computerised pump to maintain constant intragastric pH. *Gut* 1990;31:1246-9.
6. Frank W, Darlstadt R, Rockhold F. Comparison between continuous and intermittent infusion regimens of cimetidine in ulcer patients. *Clin Pharmacol Ther* 1989;46:234-9.
7. Ostro MJ, Russell JA, Soldin SJ, Mahon WA, Jeejeebhoy KN. Control of gastric pH with cimetidine: boluses versus primed infusions. *Gastroenterology* 1985;89:532-7.
8. Ballesteros MA, Hogan DL, Koss MA, Isenberg JI. Bolus or intravenous infusion of ranitidine effects on gastric pH and acid secretion: a comparison of relative efficacy and cost. *Ann Intern Med* 1990;112:334-9.
9. Sanders SW, Buchi KN, Moore JG, Bishop AL. Pharmacodynamics of intravenous ranitidine after bolus and continuous infusion in patients with healed duodenal ulcers. *Clin Pharmacol Ther* 1989;46:545-5.
10. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers: a model of the relationship between ulcer healing and acid suppression. *Gastroenterology* 1990;99:345-51.