

Continuous intravenous infusions of famotidine maintain high intragastric pH in duodenal ulcer

H S MERKI, L WITZEL, D KAUFMAN, MARION KEMPF, J NEUMANN, J RÖHMEL, AND R P WALT

From the DRK Hospital, Mark Brandenburg, Department of Gastroenterology, Berlin, FRG, Department of Gastroenterology, Inselspital, Berne, Switzerland, Department of Statistics, Arzneimittelforschung, Berlin, FRG, and Department of Medicine, University of Birmingham, Birmingham

SUMMARY Three double blind crossover studies were carried out to assess the ability of primed infusions of famotidine to raise intragastric pH over 24 hours in 12 duodenal ulcer patients. pH was measured continuously using intragastric electrodes and solid state recording devices. The studies compared the effects of placebo, famotidine 10 mg bolus injection iv followed by continuous infusions of 3.2 mg/h and 4 mg/h in random order. Gastric acidity decreased significantly with both dose regimens ($p < 0.0005$) but the effects of either dosage were similar. During fasting median pH rose from 1.35 to 7.1 and 7.05 respectively. During the day, when standard meals were taken, median pH rose from 1.30 to 4.3 and 3.65 respectively. Despite continuous infusions the H_2 -antagonist was less effective during this time. The latter finding raises questions about gastric secretory control during the day when food is eaten.

Intravenous antisecretory drugs are commonly used in patients with gastrointestinal bleeding,^{1,2} in intensive care units^{3,4} and in anaesthesia.^{5,6} The aim of such therapy is to raise the pH of the gastric milieu to a level at which peptic activity is minimal so that clot or mucosal digestion is limited. While it has been suggested that rebleeding from peptic lesions is decreased when pH rises to about pH 4,⁷ clear evidence that H_2 -receptor antagonists reduce rebleeding rates or mortality is lacking. A positive trend suggesting efficacy of cimetidine and ranitidine exists⁸ and a possible reason for such limited success is that existing dosage regimens produce less than optimum changes in gastric pH.⁹ It is clear that greater pharmacodynamic responses follow continuous infusions of H_2 -antagonists compared with bolus injections.¹⁰⁻¹⁴ We have therefore measured the effect of continuous infusions of the new H_2 -receptor antagonist, famotidine (MSD, Yamanouchi), on gastric acidity measured continuously by intragastric glass electrodes.

Methods

PATIENTS

Duodenal ulcer patients: 12 patients volunteered to undergo three separate studies. Written informed consent was obtained from each patient and the protocol was reviewed and accepted by the hospital ethical committee. The patients had all had at least one endoscopically proven episode of duodenal ulceration in the past year and healing had been confirmed. All were in symptomatic remission and nine had received no anti-ulcer therapy in the preceding month. Three patients, however, completed courses of maintenance therapy (ranitidine 150 mg nocte) three days before the start of the first experiment and remained off treatment throughout. Concomitant drug use and previous gastric surgery were exclusion criteria.

GASTRIC ACIDITY

Measurements were recorded every five seconds from intragastric combined glass electrodes (Ingold AG) onto solid state devices (Ingold AG). Calibration was done before transnasal introduction of the electrode at pH 1.67, 4.01, and 7.00 and an automatic

Address for correspondence: Dr Hans S Merki, Inselspital Berne, CH-3010 Berne, Switzerland.

Received for publication 24 September 1987.

temperature correction was applied. Drift of the electrode was accepted if less than 0.15 unit and was checked after each recording period. Detailed methods and validation have previously been published.¹⁵⁻¹⁸

The patients attended the investigation ward in groups of 12 at 0600 h having fasted from midnight the night before. A cannula was placed into a forearm vein and the electrodes were passed into the stomach. In order to simulate conditions of hospitalisation the patients were confined to bed except for meals and bathing and cigarette smoking was not allowed. pH measurements started at 0800 h and continued until 0800 h the following day. Lunch was given at 1300 h, tea at 1600 h, supper at 1800 h and a snack at 2200 h (details are available on application to the authors). The menus for each study day were identical and extra food was not allowed.

DRUG ADMINISTRATION

At 0800 a bolus injection was given over two minutes and a continuous infusion was started at a rate of 1 ml/h using mobile rechargeable pumps (Perfusor *secura*/Braun Melsungen, FRG). The studies were randomised, crossover and double blind. The following regimens were compared: (a) Placebo 10 ml bolus followed by 1 ml/h (normal saline injection); (b) Famotidine 10 mg as a 10 ml bolus followed by 3.2 mg/h (80 mg in 25 ml normal saline); (c) Famotidine 10 mg as a 10 ml bolus followed by 4.0 mg/h (100 mg in 25 ml normal saline).

Routine haematological and biochemical screening and ECG were done before and after each study and 4 hourly blood pressure and pulse measurements were made during the studies.

DATA PROCESSING AND STATISTICAL ANALYSIS

Data were transferred *via* floppy discs to a Harris computer and analysis was only done when all studies were complete. The following time periods were defined for analysis; 24 hours, fasted (0900-1300 h plus 2400-0800 h), and fed (1300-2400 h). Percentage of time with pH above 5.0 and 6.0 were defined as the primary and secondary variables of interest for statistical comparisons. Wilcoxon's signed rank tests were used for the above comparisons between all study days. Probability values of $p < 0.05$ were considered significant.

Results

The study was well tolerated and no side effects of drug administration were noted. Electrocardiographic abnormalities and significant changes in haematological and biochemical profiles were not seen. No studies were repeated through inadequate

electrode function but one day's data from one patient were lost because it was not able to be transferred from the recording device.

The mean age of the 12 patients (seven men, five women) was 45 (range 20-65) years (nine smokers, three non-smokers).

Figures 1a (placebo), b (famotidine 3.2 mg/h), and c (famotidine 4 mg/h) show all the individual 24 hour pH profiles and the median for each study day. Consistency of response was remarkable during the fasted period (only two profiles deviate far from the median during the night on active treatment), but responses were lower and less consistent during the fed period. The median pH profiles for all studies are shown in Figure 2. Median pH (interquartile range IQR) during the fasted period was 1.35 (1.1-2.0) on placebo, 7.1 (6.85-7.2) on famotidine 3.2 mg/h, and 7.05 (6.85-7.2) on famotidine 4 mg/h. During the fed period median pH (IQR) was 1.3 (1.15-1.7) on placebo, 4.3 (2.95-5.75) on famotidine 3.2 mg/h and was 3.65 (3.15-5.05) on famotidine 4 mg/h. Overall median 24 hour pH can be seen together with the above results in Figure 3. The Table shows the percentage of time pH was above the predefined levels of 5.0 and 6.0 during these time periods. Significantly reduced acidity was found with both doses compared with placebo during all time periods ($p < 0.0001$) but the small differences between the higher and lower famotidine doses were never statistically significant.

Discussion

The aim of this study was to investigate whether it was possible to raise intragastric pH to concentrations above 5.0 throughout a 24 hour period with continuous infusion of a potent H_2 -receptor antagonist. We used higher doses than those recommended for standard duodenal ulcer therapy because we were aware of difficulties others had experienced in attempts to produce prolonged anacidity in patients with H_2 -receptor antagonists.¹⁰⁻¹² The doses used here are similar in terms of potency to those used previously¹⁰ when cimetidine 100 mg/h would not maintain pH above 4.0 in over 10% of acutely ill patients. We wanted to raise pH consistently above 5 or even higher so as to limit peptic activity which may be important for prevention of stress ulceration,^{4,19-21} and prevent clot digestion which might be important in gastrointestinal bleeding.²²

We have shown consistent responses of duodenal ulcer patients to continuous infusions of famotidine. The change in pH we have measured is of similar order to that observed during intravenous omeprazole therapy.²³ Primed infusions (10 mg followed by 3.2 mg/h) raised gastric pH well into the target range

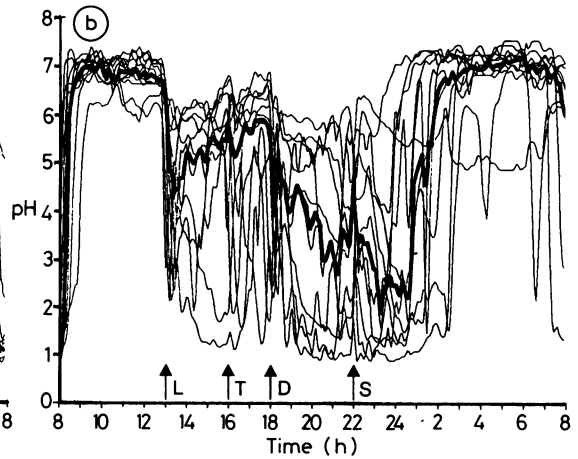
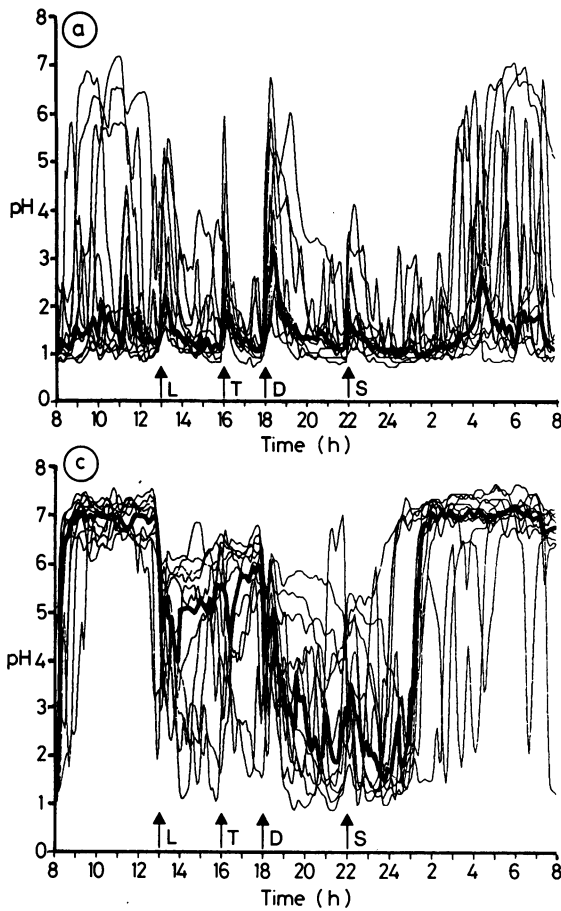


Fig. 1a 24 hour pH profiles of all patients during placebo. The individual profiles are all shown for 5 minute medians and the thick line represents the group medians. Meals are shown at the bottom by the arrows, L (lunch), T (tea), D (dinner), and S (snack). (b) 24 hour pH profiles of all patients during primed infusions of famotidine 3.2 mg/h. (c) 24 hour pH profiles of all patients during primed infusions of famotidine 4 mg/hour.

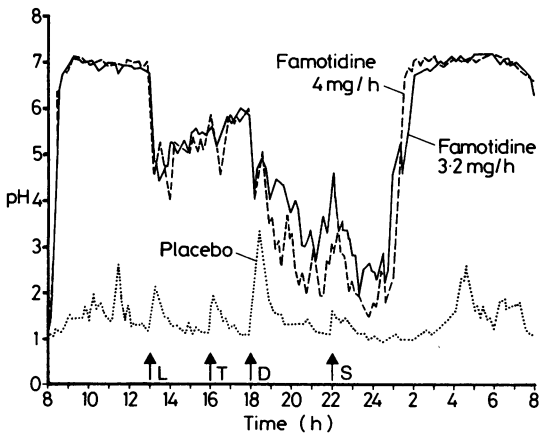


Fig. 2 Median 24 hour pH profiles during placebo (dotted line), famotidine 3.2 mg/h (solid line) and famotidine 4 mg/h (broken line). Meals are shown as for Fig. 1.

when patients were not fed. Most patients on intensive care units and many patients with significant gastrointestinal haemorrhage are kept 'nil by mouth' and for these this dosage regimen should prove effective providing extrapolation from our controlled circumstances is valid. From our results, additional clinical benefit from higher dose infusions would not be expected.

Table Percentage of time above pH 5 and 6 during all treatments at all times

	Fasted		Fed		24 hours	
	pH>5	pH>6	pH>5	pH>6	pH>5	pH>6
Pla	4.7	1.4	0.0	0.0	3.8	1.3
Fam 3.2 mg/h	86.5	84.7	42.0	7.5	69.1	49.6
Fam 4 mg/h	87.1	86.4	30.0	9.5	60.8	50.1

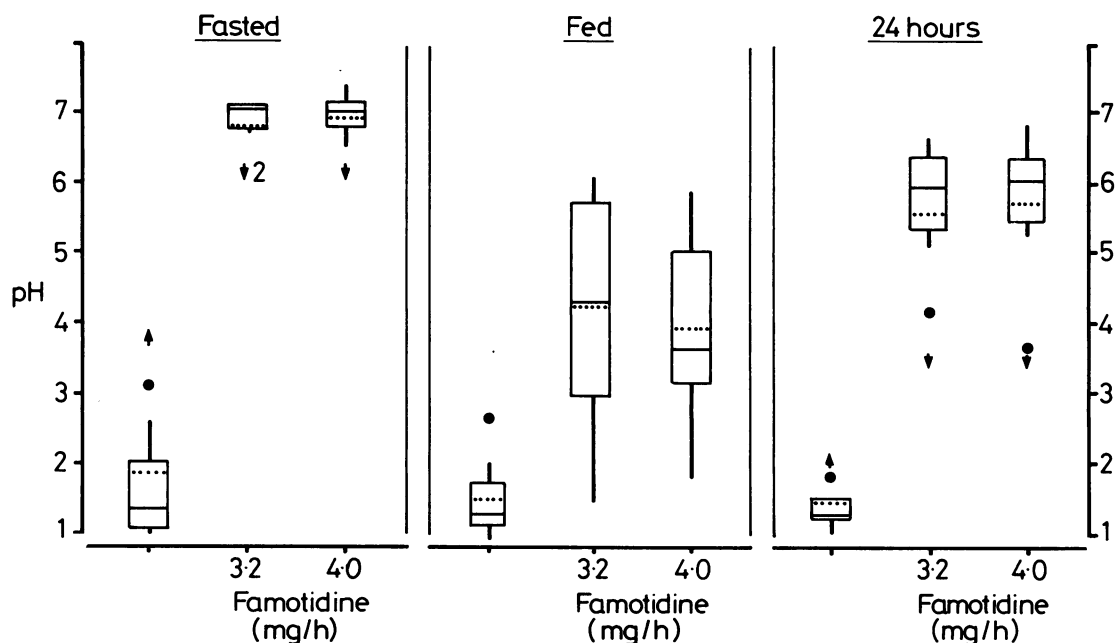


Fig. 3 Box-whisker plots of median pH values on all treatments during the 24 hours, fasted period (0900–1300 plus 2400–0800 h), and fed period (1300–2400 h). In these plots the median is shown as a solid horizontal line and the box around it represents the two quartiles. The mean is shown as a broken line. Whiskers above and below the box stretch to the furthest value within one interquartile distance from the quartiles. Values outside this range are shown separately as dots and arrows. (Full explanation in reference 17.)

In these studies we chose to feed the patients standard meals. In some countries patients admitted with gastrointestinal haemorrhage are not denied food and as far as possible we tried to simulate clinical circumstances. It was also felt that bleeding itself may provide a stimulus to gastric secretion similar to that of a high protein meal. We realised that eating may stimulate gastric acidity and affect the responses of patients to a continuous infusion of an H_2 -receptor antagonist and therefore predefined fasting and fed periods for separate analysis. We were, however, surprised by the magnitude of the change which followed food. The return of acidity occurred in the patients despite continuous infusions of famotidine which had produced virtual anacidity before eating and is best seen in Figures 2 and 3. Active drug was continuing to be administered as is clear from the return of anacidity after midnight. The consistency of our results makes it almost impossible that the findings are spurious.

It is unclear why H_2 -receptor antagonism seems less effective when patients are fed but similar findings have previously been reported.^{24,25} Many speculations are possible: food may stimulate gastric secretion through mechanisms (hormonal or neuro-

logical) which are unaffected by H_2 -receptor antagonism.

It is well known, however, that H_2 -blockade in man does inhibit food, pentagastrin, and vagally induced gastric secretion.^{26,27} The number of H_2 -receptor sites may increase in response to certain stimuli and the 'new' sites might not be adequately occupied by circulating antagonists. Nevertheless the higher dose of famotidine was not more effective during the fed period suggesting that higher concentrations of antagonist are not additionally useful. Others have found that increasing the dose (and plasma concentration) of cimetidine does not enable one to decrease acidity further in some patients.^{10,28} Famotidine, in common with ranitidine and cimetidine, is a competitive antagonist of H_2 -receptors and its antagonism is surmountable. It is possible that after food, circulating H_2 -agonist levels rise high enough to replace the antagonist at the receptor. In this case, however, one would expect increasing doses of antagonist to be more effective (although massive dosage increments may work but formal investigations are required). It is also possible that H_2 -receptor blockade might increase the sensitivity of the gastrin and cholinergic receptor. Further

investigations are required to identify the mechanisms which limit the antisecretory effects of H₂-receptor antagonists and which seem prominent during the day when people eat.

References

- 1 Hoare AM, Bradby GVH, Hawkins CF, Kane JY, Dykes PW. Cimetidine in bleeding peptic ulcer. *Lancet* 1979; ii: 671-3.
- 2 Dawson J, Cockel R. Ranitidine in acute upper gastrointestinal haemorrhage. *Br Med J* 1982; **285**: 476-7.
- 3 Herrman V, Kaminski DL. Evaluation of intragastric pH in acutely ill patients. *Arch Surg* 1979; **114**: 511-4.
- 4 Peura DA, Johnson LF. Cimetidine for prevention and treatment of gastroduodenal lesions in patients in an intensive care unit. *Ann Intern Med* 1985; **103**: 173-7.
- 5 Crawford S. Cimetidine in elective caesarian section. *Anaesthesia* 1981; **36**: 641-7.
- 6 Strunin L, Williams JG. The use of ranitidine in anaesthesia. In Riley AJ, Salmson PR, eds. *Ranitidine*. Proceedings of an international symposium held in the context of the seventh World Congress of Gastroenterology. Amsterdam: Excerpta Medica, 1982: 163-7.
- 7 Sippy BW. Gastric and duodenal ulcer. Medical care by an efficient removal of gastric juice corrosion. *JAMA* 1915; **64**: 1625-30.
- 8 Collins R, Langman M. Treatment with histamin H₂ antagonists in acute upper gastrointestinal haemorrhage. Implications of randomised trials. *N Engl J Med* 1985; **313**: 660-6.
- 9 Reynolds JR, Walt RP, Clark AG, Hardcastle JD, Langman MJS. Intragastric pH monitoring in acute upper gastrointestinal bleeding and the effect of intravenous cimetidine and ranitidine. *Aliment Pharmacol Ther* 1987; **1**: 23-30.
- 10 Ostro MJ, Russel JA, Soldin SJ, Mahon WA, Jeejeebhoy KN. Control of gastric pH with cimetidine: boluses versus primed infusions. *Gastroenterology* 1985; **89**: 532-7.
- 11 Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. 24 hour control of intragastric acidity in duodenal ulcer patients. *Lancet* 1975; ii: 1069-72.
- 12 Peterson WL, Richardson CT. Sustained fasting achlorhydria: a comparison of medical regimens. *Gastroenterology* 1985; **88**: 666-9.
- 13 Morgan DJ, Uccellini DA, Raymond K, Mihaly GW, Jones DB, Smallwood RA. The influence of duration of intravenous infusion of an acute dose on plasma concentrations of cimetidine. *Eur J Clin Pharmacol* 1983; **25**: 29-34.
- 14 Morris DL, Markham S, Beachey A, et al. Ranitidine for stress ulceration: effect of bolus or infusion administration [Abstract]. *Gut* 1985; **26**: A1106.
- 15 Fimmel CJ, Etienne A, Cilluffo T, et al. Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H₂-antagonists. *Gastroenterology* 1985; **88**: 1842-51.
- 16 Etienne A, Fimmel CJ, Bron BA, Loizeau E, Blum AL. Evaluation of pirenzepine on gastric acidity in healthy volunteers using ambulatory 24 hour intragastric pH monitoring. *Gut* 1985; **26**: 241-5.
- 17 Merki HS, Witzel L, Walt RP, et al. Day to day variation of 24 hour intragastric acidity. *Gastroenterology* (In press.)
- 18 Merki HS, Witzel L, Harre K, Scheurle E, Neumann J, Rohmel R. Single dose treatment with H₂-receptor antagonists: is bedtime administration too late? *Gut* 1987; **28**: 451-4.
- 19 Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding. *N Engl J Med* 1980; **302**: 426-30.
- 20 Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding. *N Engl J Med* 1978; **298**: 1041-5.
- 21 Zinner MJ, Zuidema GD, Smith PL, Mignosa M. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. *Surg Gynecol Obstet* 1981; **153**: 214-20.
- 22 Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation: a possible contributor to prolonged gastroduodenal mucosal haemorrhage. *Gastroenterology* 1978; **74**: 38-43.
- 23 Walt RP, Reynolds JR, Langman MJS, et al. Intravenous omeprazole rapidly raises intragastric pH. *Gut* 1985; **26**: 902-6.
- 24 Walt RP, Male PJ, Rawlings J, Hunt RH, Milton-Thompson GJ, Misiewicz JJ. Comparison of the effects of ranitidine, cimetidine and placebo on 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut* 1981; **22**: 49-54.
- 25 Merki HS, Witzel L, Walt RP, et al. Comparison of ranitidine 300 mg twice daily, 300 mg at night and placebo on 24-hour intragastric acidity of duodenal ulcer patients. *Aliment Pharmacol Ther* 1987; **1**: 217-23.
- 26 Londong W, Londong V, Ruthe C, Weizert P. Complete inhibition of food stimulated gastric acid secretion by combined application of pirenzepine and ranitidine. *Gut* 1981; **22**: 542-8.
- 27 Peden NR, Saunders JHB, Wormsley KG. Inhibition of pentagastrin-stimulated and nocturnal gastric secretion by ranitidine. *Lancet* 1979; i: 690-2.
- 28 Gledhill T, Buck M, Hunt RH. Effect of no treatment, cimetidine 1 g/day, cimetidine 2 g/day and cimetidine combined with atropine on nocturnal gastric secretion in cimetidine non-responders. *Gut* 1984; **25**: 1211-6.