

Maintenance of intragastric pH >4 with famotidine in duodenal ulcer patients: factors influencing drug requirements

J C Delchier, F Roudot-Thoraval, L Stanescu, M C Deharvengt, L Elouaer Blanc

Abstract

The gastrojet, a closed loop pH feedback infusion pump capable of maintaining intragastric pH at a target value by infusing H₂ blockers at variable rates, was used to assess factors influencing the quantity of famotidine required to maintain intragastric pH above 4 for 24 hours in 34 fed patients with duodenal ulcers. The following factors were considered: sex, age, duration of the disease, previous bleeding, previous poor response to H₂ blockers (ulcer unhealed at six weeks, or recurrence within three months during maintenance treatment), activity of the ulcer disease, smoking habits, cirrhosis. The patients had taken no antisecretory drugs for the 15 days before the study. Two standardised meals were given during the study period (from 1000 to 1000). Fifty ml of famotidine (4 mg/ml) was loaded into infusion bags and the pump was programmed to deliver the drug intravenously at 11 rates varying from 0 to 40 µl/min. The target pH was 4. Mean famotidine use was 111 mg (range 33 to 200), the 23 hour median pH was 5.3, and the mean time during which pH was above 4 was 75.4%. There was a negative correlation ($p < 0.001$) between famotidine delivery and the inhibition of gastric acidity. Statistical analysis showed that only cirrhosis significantly influenced drug delivery, median pH, and the time during which pH was above 4. Mean drug delivery in the cirrhotic and non-cirrhotic patients was 135 v 97 mg ($p < 0.04$), 23 hour median pH was 4.7 v 5.6 ($p < 0.01$), and the mean time at pH >4 was 65.9 v 81.6% ($p < 0.01$). There were large inter-individual variations in famotidine requirements, but only cirrhosis was predictive of high dose requirement. These results suggest that the appropriate amount of famotidine to treat duodenal ulcer in cirrhotic patients is probably higher than the usually recommended dose.

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receptor antagonists at usual doses is more or less rapid according to the patients. Most patients heal at four weeks, while 'slow responders' take about two months and the rare 'non-responders' do not heal despite treatment for at least three months. pH Metric studies^{2,3} showed that nocturnal control of gastric acidity is inadequate in non-responders to H₂ receptor antagonists, although the factors modulating individual secretory responses to these drugs are unclear. It has been suggested that acid suppression may be impaired in patients with basal acid output exceeding 10 mmol/h,⁴ as well as in smokers^{5,6} and in cirrhotics.⁷

Drug delivery suited to the individual patient is now possible with the gastrojet (Medical Instrument Corporation, Switzerland), a device consisting of a pH meter connected to a computerised infusion pump. Intragastric pH is continuously monitored and the rate of drug delivery is adjusted to maintain it at a programmed value. Using the gastrojet, famotidine, the most potent H₂ receptor antagonist, can maintain pH above 6 in fasting healthy subjects⁸ and overcome gastric acid secretion stimulated by food.⁹

We used the gastrojet to assess factors influencing the amount of famotidine required to maintain intragastric pH above 4 over 24 hours in duodenal ulcer patients.

Patients and methods

PATIENTS

Thirty four patients referred to our endoscopy unit for the investigation of duodenal ulcers participated in the study; 20 had an overt ulcer at endoscopy, while the remaining 14 were in remission from an ulcer seen endoscopically in the previous 12 months. All antisecretory drugs had been discontinued for at least 15

TABLE 1 Main characteristics of the patients (n=34)

Mean age (y) (range)	50 (26-69)
Sex (F/M)	5/29
Mean weight (kg) (range)	66 (48-100)
Mean duration of ulcer disease (y) (range)	5 (0-15)
Previous bleeding	13 (38%)
Previous history of poor response to H ₂ blockers	10 (40%)*
Active ulcer	20 (59%)
Smokers	15 (44%)
Cirrhosis (Child-Pugh grade B/C)	13 (38%)

*Results of previous treatment could be evaluated in only 25 patients. The other nine patients were attending for a first attack of peptic ulcer disease.

Unité INSERM 99 et Service d'Hépatogastro-entérologie, Hôpital Henri Mondor, Créteil, France
J C Delchier
F Roudot-Thoraval,
L Stanescu,
M C Deharvengt,
L Elouaer Blanc

Correspondence to:
Dr J C Delchier, Service d'Hépatogastroentérologie, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France.

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It is now well established that the rapidity of duodenal ulcer healing with antisecretory drugs is related to the degree of 24 hour gastric acid suppression.¹ The speed of healing of duodenal ulcers in patients treated with H₂

TABLE II Famotidine delivery and pH control in the 34 patients

24 hour famotidine delivery (mg)	
(mean (SD) range)	
Calculated	111 (46) (36-210)
Weighted	111 (44) (33-200)
Intragastric pH	
(median, interquartile range)	
23 hour period	5.3 (4.8-5.8)
8 hour nocturnal period	5.2 (4.0-5.8)
Per cent of time at pH >4	
(mean (SD))	
23 hour period	75.4 (16)
8 hour nocturnal period	66.3 (32)

days before the study; if required, they were replaced with sucralfate 1 g twice daily. All the patients had plasma creatinine value below $<120 \mu\text{mol/l}$. The study protocol was approved by the Hôpital Henry Mondor ethics committee and written informed consent was obtained from all participants. Table I shows the main characteristics of the study population.

Poor response to H_2 receptor antagonists was defined as a lack of healing after six weeks of treatment at the usual doses or relapse during maintenance treatment within three months of healing. The results of previous treatment with H_2 receptor antagonist could be evaluated in 25 patients; the remaining nine were attending for a first attack of peptic ulcer disease. Thirteen patients had cirrhosis diagnosed on the basis of histological examination or typical laboratory test results and clinical signs (oesophageal varices, ascite), or both. According to Child-Pugh criteria, nine patients had class B and four had class C cirrhosis. At the time of the study, cirrhotic patients were not confined to their bed and non of them had either infection or anaemia (haemoglobin $<100 \text{ g/l}$).

THE GASTROJET PROCEDURE

An exact amount of 200 mg famotidine in 50 ml of 5% dextrose was prepared and loaded into special plastic infusion bags. The gastrojet was programmed to infuse the drug at 11 different rate settings, from 0 to 160 $\mu\text{g/min}$ (0 to 40 $\mu\text{l/min}$), in 16 $\mu\text{g/min}$ steps. The built in monitoring system records pH in the stomach every six seconds by a combined glass electrode (Ingold M 440, Switzerland). The infusion rates were automatically adjusted to maintain intragastric pH at a target value of 4 after a fixed rate period of one hour at 20 $\mu\text{l/min}$ (80 $\mu\text{g/min}$). The rate was increased every four minutes if the pH fell below the target pH and reduced every 28 minutes if it remained above the target pH.

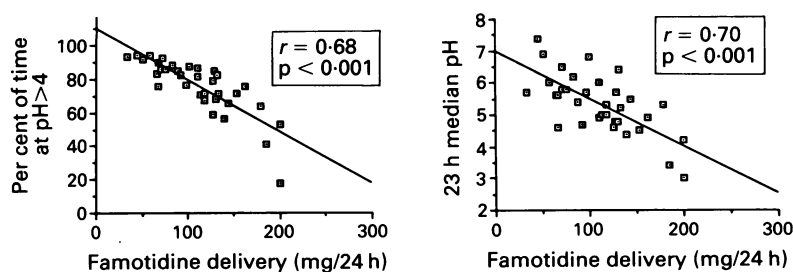


Figure 1: Correlation of 24 hour famotidine delivery with per cent of 23 hours at pH >4 and 23 hour median pH.

PROCEDURE

All the patients had fasted for 12 hours before the study. After calibration, the Ingold glass electrode was passed through the nose into the stomach at 9 30 am and placed, with fluoroscopic control, 10 cm under the cardia; it was then fixed in place and connected to the gastrojet. Two litres of 5% dextrose were infused over the 24 hour study period by an intravenous catheter. Famotidine was delivered through an extension catheter connected to the infusion tube by a three way tap.

The gastrojet was set to run from 1000 until 1000 the following day. Two standard meals were supplied at 1230 and 1830. The patients were allowed to drink water and to move about in the hospital ward, but not to smoke or drink coffee and alcohol. At the end of each study period, it was checked that electrode drift was $<0.1 \text{ pH unit}$.

DATA ANALYSIS

Individual data were processed on an IBM XT computer. The pack 2/gastro software calculated mean and median pH (interquartile range) and the proportion of time at which pH was above 4. The periods analysed were from 1100 to 1000, and from 2200 to 0600 hours. The 24 hour pH profile, changes in the drug delivery rate, and the time held at each infusion rate were recorded. Drug delivery was calculated from the recorded infusion rates and compared with that measured by weighing the infusion bag at the beginning and at the end of the study period.

As the parameters studied were not normally distributed, non-parametric tests were used (Kruskal-Wallis analysis of variance or Spearman's correlation test for quantitative variables). Multivariate analysis was not performed because only one factor was significantly related to the parameters studied.

Results

OVERALL GROUP

No adverse events were reported by the patients, all of whom completed the study.

Table II gives the famotidine delivery and gastric pH metric data. The calculated total amount of drug infused was always slightly different from that measured by weighing but the difference never exceeded 14% (mean 6.9%). In three cases, the infusion bag was emptied before the end of the study period and the delivery calculated from the micropump exceeded 200 mg; we therefore used weight derived doses for data analysis.

The relation between the amount of famotidine delivered over 24 hours and the control of gastric acidity was studied by plotting famotidine delivery (mg) against both the median 23 hour pH and the proportion of time during which gastric pH was above 4. As Figure 1 shows, there was a negative correlation between famotidine delivery and the rate of acid suppression.

TABLE III Influence of cirrhosis on intragastric pH control and famotidine delivery

	Cirrhotic patients (n=13)	Non-cirrhotic patients (n=21)
Intragastric pH (median, interquartile range)		
23 Hour period	4.7 (4.5-5.5)*	5.6 (5.2-6.0)
8 Hour nocturnal period	4.0 (3.6-4.6)*	5.6 (4.7-5.9)
Per cent of time at pH >4 (mean (SD))		
23 Hour period	65.9 (19.3)*	81.6 (10.6)
8 Hour nocturnal period	48.7 (31.5)*	77.8 (27.2)
24 Hour famotidine delivery (mg) (mean (SD) range)	135 (50)** (72-200)	97 (38) (49-170)

*Significantly different from the non-cirrhotic patients ($p < 0.01$); **significantly different from the non-cirrhotic patients ($p < 0.04$).

FACTORS POTENTIALLY INFLUENCING FAMOTIDINE DELIVERY AND INTRAGASTRIC pH CONTROL

Age, weight, sex, duration of the disease, previous bleeding or resistance to H_2 blockers, disease activity, and smoking did not significantly influence drug delivery or intragastric pH control.

Both drug delivery and intragastric pH control were, however, influenced by cirrhosis (Table III). The 24 hour famotidine delivery was significantly higher ($p < 0.04$) in cirrhotic patients than in patients without cirrhosis. Median intragastric pH was significantly lower ($p < 0.01$) in cirrhotic patients than in non-cirrhotic patients during both 23 hours and nocturnal period. The per cent of time at pH above 4 was also significantly lower ($p < 0.01$) in cirrhotic patients than in non-cirrhotic patients in both study periods. Figure 2 shows the 24 hour median pH profiles and the 24 hour mean famotidine delivery rate profiles in cirrhotic and non cirrhotic patients. In non-cirrhotic patients, the pH profile was

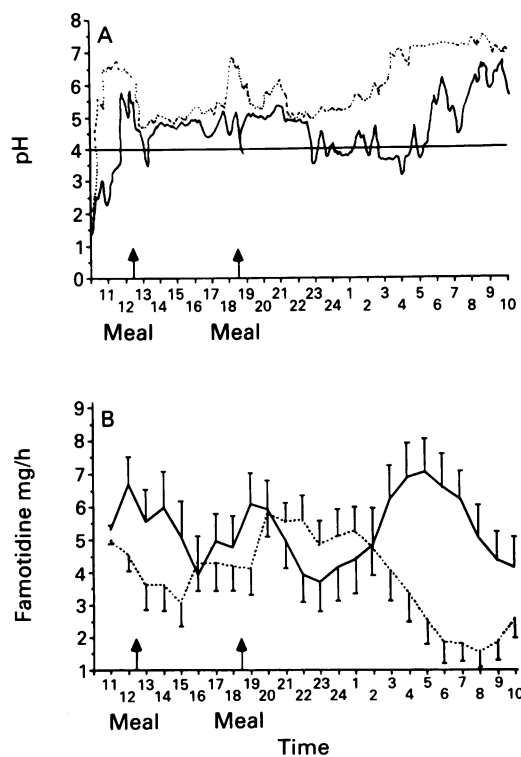


Figure 2: (A) Median 24 hour pH profiles; (B) mean (SD) 24 hour famotidine delivery profiles in cirrhotic (—) and non-cirrhotic (-----).

characterised by brief postprandial rises and by a prolonged rise late at night while the famotidine delivery profile was characterised by a fall late at night. In cirrhotic patients, nocturnal rise of pH was delayed and was preceded by a comparative fall although famotidine delivery rates increased considerably to reach a peak at 0600. Mean (SD) famotidine delivery rate during the period from 3 to 10 hours was of 2.4 (2.4) mg/hour in non-cirrhotic patients and of 6.0 (3.1) mg/hour in cirrhotic patients ($p < 0.01$). In two patients with cirrhosis, it could be calculated that the plastic bag containing 200 mg famotidine was emptied 186 minutes and 30 minutes respectively before the end of the study period. Mean (SD) famotidine requirements were not significantly different in patients who had class B or class C cirrhosis according to the Child-Pugh classification: 156 mg (25) *v* 127 mg (54). The two patients who required more than 200 mg of famotidine had class B cirrhosis.

Discussion

The gastrojet is a useful tool to assess factors influencing response to H_2 blockers by assessing the amount of drug required for individual patients to maintain gastric pH above a target pH. In this study, a high target pH (pH 4) was chosen to potentiate interindividual variations in response to famotidine.

Famotidine delivered by the pH feedback microinfusion pump maintained intragastric pH above 4 for more than 75% of the 24 hour study in a group of 34 patients with duodenal ulcer disease. The amount of drug delivered (mean 111 mg) was very large compared with the oral therapeutic dose of 40 mg after dinner, which produces effective suppression of nocturnal acid secretion. A comparative resistance to H_2 blockade during the diurnal period could be related to a 'food effect'. Indeed, food drastically reduces the pharmacodynamic efficacy of H_2 blockers given both orally¹⁰ and intravenously¹¹ and large doses are required to overcome this negative effect.⁹

Despite the possibility of delivering large doses of famotidine, the gastrojet failed to maintain gastric pH above the target value in every patient for all the study period. This may have been partly because of the limited adaptability of the drug infusion system. This was mainly related, however, to a poor response to famotidine in some patients as well illustrated by the negative correlation between drug delivery and adequacy of gastric acid suppression. This finding is consistent with the previously reported absence of benefit of increasing the dose of H_2 receptor antagonists given orally in patients in whom acidity is not adequately inhibited by usual doses.^{2,7}

There were wide interindividual variations in drug requirements (33 to 200 mg). Although only cirrhosis was found to have any influence, other factors may have gone unnoticed because of the small size of the group studied. Age and sex, however, have previously been shown not to affect patterns of

intragastric acidity in duodenal ulcer disease,¹² while gastric acid secretion does not differ in patients with overt ulcers and those in remission.¹³ In addition, there is no evidence of hyperacidity in patients with a past history of bleeding from ulcers and the duration of the disease does not influence response to H₂ blockers according to Sonnenberg *et al.*¹⁴

At first sight, the results in the group of patients with a past history of poor response to H₂ blockers were surprising, as several authors have reported increased basal acid output^{4 15} or impaired antisecretory response,^{2 3} or both in patients whose ulcers failed to heal with a conventional course of H₂ blockers. Bardhan¹⁶ reported, however, that neither gastric acid secretion or the degree of inhibition by H₂ receptor antagonists differed in patients with refractory and responsive disease. Smoking is the most important factor that delays healing and favours the recurrence of duodenal ulcers in patients treated with the H₂ receptor antagonists.^{17 18} Bauerfeind *et al.*⁶ showed that H₂ receptor antagonists were slightly less effective in smokers than in non-smokers but concluded that this could not explain the unfavourable effect of smoking on peptic ulcer healing in patients treated with antisecretory drugs. Our results confirm that the unfavourable effect of smoking is not principally mediated by a decrease in the antisecretory response and favour a defect in mucosal defences as the main cause of resistance to H₂ blockers.

Gastric acidity was less well inhibited in patients with cirrhosis than in those with normal liver despite delivery of a larger dose of famotidine (in two cirrhotic patients, the infusion bag (200 mg) was emptied before the end of the 24 hour period study). These results confirmed those of Walker *et al.*⁷ who showed that nocturnal pH control was often impaired in cirrhotic patients treated with H₂ blockers for various ulcerated lesions, and are of particular clinical importance given the high prevalence of upper gastroduodenal ulcerations in cirrhotic patients.¹⁹ From a pharmacokinetic point of view, cirrhosis should favour the antisecretory effect, as impaired hepatic clearance contributes to increasing plasma drug concentrations. Previous studies have shown increased^{20 21} or unchanged²² plasma concentrations of H₂ blockers in cirrhotic patients relative to values in patients with normal livers. Inadequate control of gastric acidity in cirrhotic patients is not related to hypersecretion, as normal²³ or decreased²⁴ gastric acid secretion has been reported. Several possible explanations for the unresponsiveness to H₂ blocker in some cirrhotic patients have been previously proposed: a change in number or sensitivity, or both of the H₂ receptors on parietal cells, diminished prostaglandin content in gastric mucosa,²⁵ etc. Our data suggest modifications in circadian rhythm of gastric secretion in cirrhotic patients. In non-cirrhotic patients, we indeed saw a 24 hour pH profile resembling that previously reported in healthy subjects and duodenal ulcer patients – that is, high acidity

concentration in the late evening and in the first half of the night and reduced acidity in the second part of the night.¹³ Famotidine delivery profile was also similar to that previously reported by Hannan *et al.* using famotidine infusion intravenously monitored by gastrojet to maintain intragastric pH at 6 in fasting healthy subjects: a clear trend for delivery rates to be turned down to a nadir in the early morning was seen. On the contrary, in cirrhotic patients, pH decreased despite a noticeable increase in famotidine delivery rates during this period. These findings could be related to an increased nocturnal vagal tone as it has been previously shown that increased vagal tone could considerably interact with the antisecretory effect of H₂ blockers.^{26 27} Gastric acid secretion could be one of the numerous biological parameters that have a changed circadian rhythm in cirrhotic patients.^{28 29}

Influence of cirrhosis on duodenal ulcer healing with H₂ blockers has not been evaluated in large series. Low healing rates and high relapse rates have, however, been reported.³⁰ Our results suggest that treatment failures could be related to an inadequate control of acid secretion with the usually recommended dose.

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