

Double blind comparison of the effects of cimetidine, ranitidine, famotidine, and placebo on intragastric acidity in 30 normal volunteers

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SUMMARY Continuous measurement of 24 hour intragastric acidity was carried out in 30 normal volunteers during treatment with placebo, cimetidine 800 mg, ranitidine 300 mg, and famotidine 40 mg in a double blind study. Medication was taken after the evening meal (post cenam nocte, PCN). Median 24 hour acidity decreased with all H₂-receptor antagonists from 25.1 mmol/l on placebo to 10 mmol/l (-60.1%) during cimetidine, to 3.2 mmol/l (-87.25%) during ranitidine and to 2.5 mmol/l (-90.0%) during famotidine treatment ($p < 0.0005$). All drugs significantly inhibited night time acidity but only famotidine decreased acidity during the late morning compared with placebo. Significantly greater acid reduction was seen with famotidine and ranitidine compared with cimetidine but no difference was found between famotidine and ranitidine.

It has become standard practice to assess the effects of new antisecretory agents by measuring gastric acidity over 24 hours.¹⁻¹¹ Famotidine is a new H₂-receptor antagonist which is more potent than ranitidine (approximately eight times weight for weight).¹²⁻¹⁵ Early clinical results with famotidine show it to be as effective as either cimetidine or ranitidine.^{16, 17} No previous study, however, has compared the effects of single doses of these three drugs on 24 hour gastric acidity in a double blind study of adequate size although in one study of seven subjects, famotidine 40 mg appeared more effective in reducing nocturnal acidity than ranitidine 300 mg.¹⁸ We have done repeated studies of 24 hour acidity in 30 volunteers in order to be confident that observed differences were real.

Methods

SUBJECTS

Thirty healthy volunteers (15 women, 15 men) each underwent four separate 24 hour studies at least one

week apart in Berlin. Half the subjects were non-smokers and the mean age was 25.5 years (19-39 range). Clinical, biochemical and haematological parameters were normal before study and all subjects gave informed consent. Ethical committee approval for the study was obtained before the start. Subjects took apparently identical capsules containing cimetidine 800 mg, ranitidine 300 mg, famotidine 40 mg or placebo in random order at 1900 h after the evening meal. No other drugs were allowed during the study which compared single doses of the H₂-receptor antagonists.

The technique used for the measurement of 24 hour acidity has been previously described.^{19, 20} Normal fixed diets were used unrestricted after the first four hours. Drugs were administered in the investigation ward and thereafter subjects returned to their own homes, intragastric acidity being monitored continuously using intragastric electrodes allowing accurate and reproducible measurements.^{10, 11, 20} Each study started at 1500 h and lasted until 1500 h the next day.

Results have been displayed as frequency distribution and time sequence arrays of pH values and as medians, means, and ranges (Box-Whisker-Plots).

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Received for publication 10 June 1987.

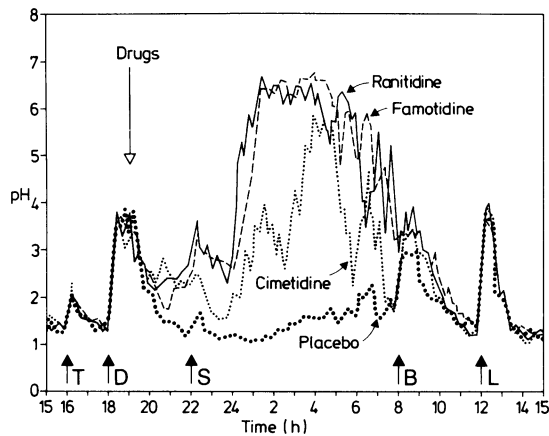


Fig. 1 Median 24 hour intragastric acidity in 30 normal volunteers receiving placebo, cimetidine 800 mg, ranitidine 300 mg and famotidine 40 mg. Median five min values are plotted. Drugs were taken as shown at 1900 h and meal times are shown at the bottom, tea (T), dinner (D), snack (S), breakfast (B), and lunch (L).

Median pH during the four treatments was compared for the following predefined time periods, 24 hours, night (2200–0600), early morning (0600–1000), late morning (1000–1200) and afternoon (1200–1500). Wilcoxon's signed rank tests were applied with correction of significance for multiple testing when appropriate.

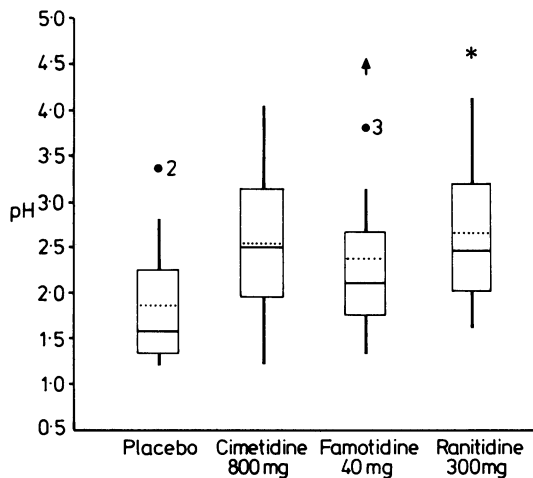


Fig. 2 Box-whisker-plots of evening acidity (1800–2200) during all treatments. The box shows the median (solid line), the mean (dotted line) and the interquartile ranges (extremes of box). Whiskers show the greatest or smallest values within one interquartile distance from the quartiles. Outliers are shown separately.²⁵ Similar plots are shown in Figures 3 and 4. All drugs decreased acidity compared with placebo but statistical testing of these differences was not done as it had not been planned in the protocol.

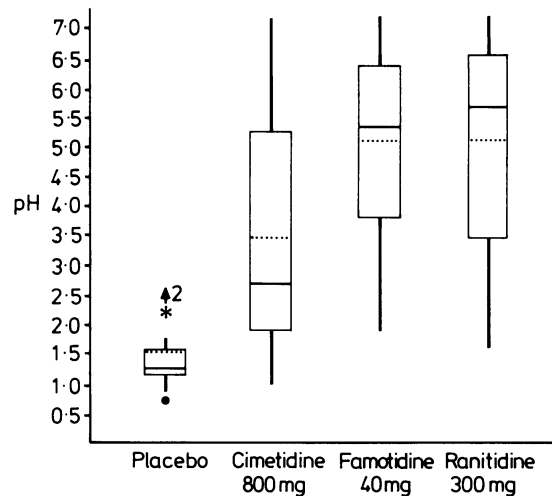


Fig. 3 Box-whisker-plots of night time acidity (2200–0600) during all treatments. All drugs produced significant inhibition of acidity compared with placebo ($p < 0.0005$) and ranitidine and famotidine had significantly greater effects than cimetidine ($p < 0.005$).

Results

The median pH profile of the 30 subjects are shown for the four treatments in Figure 1. All H_2 -receptor antagonists inhibited 24 hour acidity compared with placebo ($p < 0.0005$). Median 24 hour acidity was 25.1 mmol/l (44.7–15.8 interquartile range) on

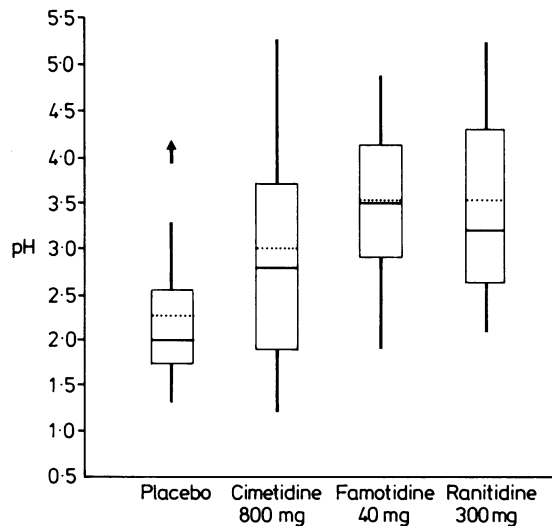


Fig. 4 Box-whisker-plots of acidity in the early morning (0600–1000) during all treatments. All drugs produced significant inhibition of acidity compared with placebo ($p < 0.005$).

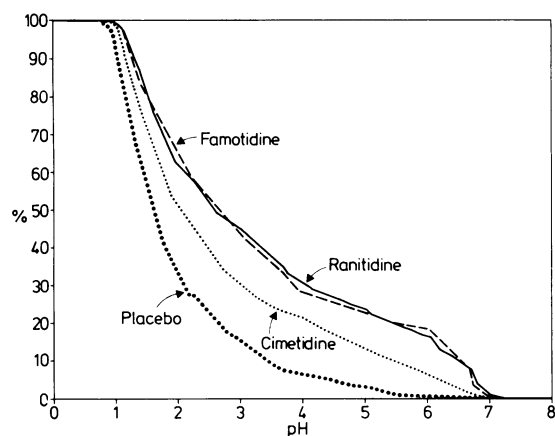


Fig. 5 Frequency distribution curves of pH in 30 normal volunteers receiving H_2 -receptor antagonists. The proportion of time during 24 hours with pH values above any given level are shown.

placebo, and decreased after cimetidine 800 mg to 10 mmol/l (15.8–6.6), after ranitidine 300 mg to 3.2 mmol/l (5.6–1.0) and after famotidine 40 mg to 2.5 mmol/l (5.6–1.0). The effect of cimetidine was significantly less than either ranitidine or famotidine ($p < 0.001$), but there was no significant difference between famotidine and ranitidine during any predefined time period. Box-whisker-plots showing the distribution, median, interquartile ranges and means for the evening (Fig. 2), night (Fig. 3) and the early morning acidity (Fig. 4) are shown. All three drugs significantly decreased gastric acidity during the latter two periods compared with placebo ($p < 0.005$). During the late morning (1000–1200) median pH was 1.5 with placebo, 1.3 with cimetidine (NS), 1.5 with ranitidine (NS) and, after a consistent response with famotidine, was 1.7 (significant compared with placebo ($p < 0.005$)). No significant inhibition of acidity was found with any drug during the afternoon. The pH frequency distribution curves (Fig. 5) clearly show that the overall effects of ranitidine and famotidine are indistinguishable.

Discussion

Continuous intragastric pH monitoring is becoming more popular as an accurate assessment of gastric pH over prolonged periods. The equipment and technique used here have been validated^{10,11} and are able to detect changes of pH during predefined time periods of 0.1 unit or greater.²⁰ In common with other methods where only pH is measured the volume of gastric secretion cannot be assessed and information about peptic activity and bile salt concentrations is not collected. Important information about the

effects of antisecretory drugs has previously been successfully collected by this and other techniques assessing only intragastric pH.^{1-11, 19, 21}

This study confirms that famotidine and ranitidine are more potent inhibitors of gastric acidity than cimetidine. In the recommended dosages for clinical use, ranitidine and famotidine decrease 24 hour intragastric acidity to a similar degree. We have not been able to confirm the findings of a small study which suggested that famotidine 40 mg was more effective than ranitidine 300 mg during the night when taken in the early evening.¹⁸ Famotidine 40 mg had significant activity over a slightly longer time period than the other drugs. Although this effect was small and possibly unimportant, the size of this study was adequate to detect such a change. No antisecretory effects, however, were found after midday with any drug.

Post cenam nocte dosing is not the standard recommended regimen for these drugs. Five separate studies have now shown that inhibition of gastric acidity during the evening and night is significantly greater after early evening dosing with H_2 -receptor antagonists compared with 'bedtime' dosing.^{18, 19, 21, 22} Pounder RE (personal communication). The more potent drugs given in adequate doses show this best while the activity of the least potent (cimetidine) weakens towards the morning and PCN dosing with 800 mg cimetidine would not be recommended. A similar increased effect is possible, however, with cimetidine given in a large dose (1600 mg).²² Although the majority of these studies were done on normal volunteers it seems reasonable to extrapolate the findings to ulcer patients as it appears that data from normal volunteers do predict the responses of ulcer patients.²³ Preliminary data also suggest that this increased pharmacodynamic effect is associated with better clinical results.²⁴ On the basis of these findings it is likely that famotidine and ranitidine would be equally effective in ulcer healing when prescribed in these PCN doses.

References

- 1 Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. 24-hour control of intragastric acidity by cimetidine in duodenal ulcer patients. *Lancet* 1975; ii: 1069–72.
- 2 Pounder RE, Hunt RH, Vincent SH, Milton-Thompson GJ, Misiewicz JJ. 24-hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine. *Gut* 1977; 18: 85–90.
- 3 Peterson WL, Barnett C, Feldman M, Richardson CT. Reduction of 24-hour intragastric acidity with combination drug therapy in patients with duodenal ulcer. *Gastroenterology* 1979; 77: 1015–20.

- 4 Walt RP, Male JP, Rawlings J, Hunt RH, Milton-Thompson GJ, Misiewicz JJ. Comparison of the effects of ranitidine, cimetidine and placebo on the 24-hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut* 1981; **22**: 49–54.
- 5 Walt RP, Gomes M, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24-hour intragastric acidity. *Br Med J* 1983; **287**: 12–4.
- 6 Gledhill T, Howard OM, Buck M, Paul A, Hunt RH. Single nocturnal dose of an H₂-receptor antagonist for treatment of duodenal ulcer. *Gut* 1983; **24**: 904–8.
- 7 Gledhill T, Buck M, Paul A, Hunt RH. Cimetidine or vagotomy? Comparison of the effects of proximal gastric vagotomy, cimetidine or placebo on nocturnal intragastric acidity and acid secretion in patients with cimetidine resistant duodenal ulcer. *Br J Surg* 1983; **70**: 704–6.
- 8 Sharma BK, Walt RP, Pounder RE, Gomes M, Wood EC, Logan KH. Optimal dose of oral omeprazole for maximal 24-hour decrease of intragastric acidity. *Gut* 1984; **25**: 957–64.
- 9 Prichard PJ, Yeomans ND, Mihaly GW, *et al*. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening doses. *Gastroenterology* 1985; **88**: 64–9.
- 10 Etienne A, Fimmel CJ, Bron BA, Loizeau E, Blum A. Evaluation of pirenzepine on gastric acidity in healthy volunteers using ambulatory 24-hour intragastric pH-monitoring. *Gut* 1985; **26**: 241–5.
- 11 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.
- 12 Damman HG, Walter THA, Müller P, Simon B. H₂-Rezeptor-Antagonisten und intragastrale Acidität. *Dtsch Med Wochenschr* 1984; **109**: 1767–9.
- 13 McCallum RW, Kuljian B, Chremos AN, Tupy-Visich, Huber PB. Prolonged gastric antisecretory effect of a novel H₂-receptor inhibitor, MK-208 [Abstract]. *Gastroenterology* 1983; **84**: 1245.
- 14 Shiratori K, Watanabe S, Maruyama M, Kurokawa K, Takeuchi T. Effect of famotidine on gastric secretion, and on 24-hour intragastric pH in duodenal ulcer patients [Abstract]. *Gastroenterology* 1984; **86**: 1250.
- 15 Smith JL. Clinical pharmacology of famotidine. *Digestion* 1985; **32**: suppl 1: 15–23.
- 16 Simon B, Damman HG, Jakob G, *et al*. Famotidine versus ranitidine for the short term treatment of duodenal ulcer. *Digestion* 1985; **32**: suppl 1: 32–7.
- 17 Paoluzi P, Torsoli A, Bianchi Porro G, *et al*. Famotidine in the treatment of gastric ulcer. Results of a multicenter double-blind controlled study. *Digestion* 1985; **32**: suppl 1: 38–44.
- 18 Bauerfeind P, Cilluffo T, Emde C, *et al*. H₂-antagonists are more effective after early evening intake than after late intake [Abstract]. *Gastroenterology* 1986; **90**: 1340.
- 19 Merki HS, Witzel L, Harre K, Scheurle E, Neumann J., Röhmel J. Single dose treatment with H₂-receptor antagonists: Is bedtime administration too late? *Gut* 1987; **28**: 451–4.
- 20 Merki HS, Witzel L, Walt RP, *et al*. Day to day variation of 24-hour intragastric acidity. *Gastroenterology* (In press).
- 21 Warzee PL, Coppens JP, Fiasse R, Dive CH. Ranitidine single dose 300 mg. Influence of the time of administration on gastric acidity [Abstract]. *Dig Dis Sci* 1986; **31**: suppl: 333.
- 22 Deakin M, Glenny H, Ramage JK, *et al*. Treatment of duodenal ulcer by H₂ blockade, large single daily dose, how much and when? [Abstract]. *Gut* 1985; **26**: A1120.
- 23 Howden CW, Jones DB, Burget DW, Hunt RH. Comparison of the effects of gastric antisecretory agents in healthy volunteers and patients with duodenal ulcer. *Gut* 1986; **27**: 1058–61.
- 24 Merki HS, Witzel L, Hüttemann W, *et al*. Single dose treatment with H₂-receptor antagonists. A comparison of an early evening dose vs bedtime administration of ranitidine in the treatment of duodenal ulcer [Abstract]. *Gastroenterology* 1986; **90**: 1550.
- 25 McGill R, Tukey JW, Larsen WA. Variations of box plots. *Am Statistician* 1978; **32**: 12–7.