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 cenan 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.16-19 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).
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.

Results

The median pH profile of the 30 subjects are shown for the four treatments in Figure 1. All H₂-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
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Fig. 5 Frequency distribution curves of pH in 30 normal volunteers receiving H₂-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 pre-defined 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 and are able to detect changes of pH during predefined time periods of 0-1 unit or greater. 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.

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. 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 H₂-receptor antagonists compared with 'bedtime' dosing, 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). 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. Preliminary data also suggest that this increased pharmacodynamic effect is associated with better clinical results. 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

81 Merki, Witzel, Walt, Neumann, Scheurle, Mappes, Krammisch, Heim, Kaufmann, and Roehmel


