

Single dose treatment with H₂ receptor antagonists: is bedtime administration too late?

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SUMMARY Using ambulatory pH-metry, intragastric acidity was measured over three separate 24 hour periods in each of 12 healthy volunteers receiving either (a) placebo (1800 h and 2200 h), (b) 300 mg ranitidine (1800 h) and placebo (2200 h), or (c) placebo (1800 h) and 300 mg ranitidine (2200 h). Ranitidine was significantly more effective in decreasing 24 h median intragastric acidity when the drug was administered at 1800 h rather than at 2200 h. Median pH (and interquartile range) was 1.45 (1.4-1.7) on placebo, 2.55 (2.05-3.2) on ranitidine given at 2200 h and 3.35 (2.5-3.85) on ranitidine given at 1800 h ($p < 0.004$). The total duration of highly acidic electrode readings ($\text{pH} < 1.5$) over a 24 h period was reduced significantly by administering the H₂-receptor antagonist at 1800 h compared with the later administration. It is suggested that treatment of duodenal ulcers by single administration of ranitidine in the early evening should be evaluated by clinical trial.

Pharmacological and clinical studies have shown that a large single dose of H₂-receptor antagonists is at least as good as the twice daily administration in (a) decreasing 24 h intragastric acidity and nocturnal acid output and (b) healing duodenal ulcers.¹⁻³ The current recommended single dose for ranitidine is 300 mg at bedtime. In a recent study⁴ in our department 46 untreated duodenal ulcer patients were compared with 40 healthy volunteers using the new method of ambulatory intragastric pH-metry. Some previous reports have claimed that the highest acid concentration in patients with duodenal ulcer (DU) is around midnight or shortly thereafter.^{1,5} Our data⁴ show a much longer duration of constantly high acidic electrode readings ($\text{pH} < 1.5$) beginning in the early evening (1900 h) and lasting until early morning (0400 h). The results in healthy subjects agree well with earlier reports using the aspiration technique as well as pH-metry.^{6,7,9}

These findings suggest that the current practise of administering antisecretory drugs at bedtime might

be too late to control gastric acidity in an optimal manner. The aim of the present study was to evaluate the effect of an early evening dose of ranitidine on 24 h intragastric acidity and to compare it with conventional administration of the drug before sleep.

Methods

SUBJECTS

Twelve healthy volunteers (six women, six men, median age 27 years) received, on a given test day, one of the following: placebo (1800 h)+placebo (2200 h), placebo (1800 h)+300 mg ranitidine (2200 h) or 300 mg ranitidine (1800 h)+placebo (2200 h). The study was randomised, double blind and double dummy. None of the subjects had a history of gastrointestinal disease nor were they on any medication. Three women and three men were smokers. All volunteers gave informed consent and the study was approved by the Hospital Ethics Committee.

GASTRIC ACIDITY

Gastric pH was measured every five seconds by miniature combined glass electrodes (diameter

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4 mm, model '440 M4', W Ingold AG, Urdorf, Switzerland), connected to a solid state storage unit with an 18 K-byte memory (CM 18 pH, Ingold AG, Switzerland). This pH monitoring system has recently been validated by Fimmel, Etienne and Blum.^{6,10} The electrodes and the recorder were calibrated at 20°C using commercial buffer solutions of pH 7.00, 4.01, and 1.679 (Ingold AG). There was an automatic temperature correction for intragastric readings (37°C). After each run, calibration was repeated for assessment of electrode stability.

In agreement with previous reports^{6,10} the drift of the electrodes was negligible (<0.1 pH after 24 h). The subjects were admitted to a special ward at 1530 h having fasted from noon. The electrodes were passed transnasally and positioned into the gastric corpus under fluoroscopic control. The tip of the glass electrode was situated 8–10 cm below the cardia. The distance of the measuring tip to the nares was recorded and kept constant for repeated studies in each subject. Measurements began at 1600 h and lasted for 24 hours.

Volunteers ate standardised meals and a banana at the same time on each study day, and the number of cigarettes and drinks consumed was recorded and repeated on subsequent study days. Two tablets of ranitidine (150 mg) or placebo were administered by mouth after dinner (1815 h) and after a banana (2215 h). Blood samples for ranitidine radioimmunoassay (carried out in the laboratories of Glaxo, France) were measured at 1800, 2000, 2200, 2400, 0200, 0400, 0600, 0800, and at 1200 h. All subjects were allowed to move around the hospital ward during the study days.

DATA PROCESSING AND STATISTICAL ANALYSIS

At the end of each run, the five second pH readings (a total of 17 281 readings over 24 hours) were transferred to floppy disks using a Fujitsu computer (Micro 16 s).

Statistical analysis was performed after a second transfer of the data to a Harris computer (HS80) using the A programming language (APL). Separate calculations were done for the afternoon (1600–1800 h), the evening (1800–2200 h), the night (2200–0600 h), the day (0600–1600 h) and the whole 24 hour period (1600–1600 h).

Percentile pH (including median pH) and mean pH were calculated for all the periods described above. The different drug regimens were compared using the Wilcoxon's signed-rank-test. The exact distribution was calculated by the algorithm of Streitberg/Röhmel.¹¹ Carryover effects were ignored since presumably non-existent. Since 10 tests were performed, an alpha-adjustment according to Holm-Bonferroni¹² was applied. For graphs, the mean pH

of 60 pH readings (mean of five minutes) was calculated and smoothed according to Hamming.¹³

Results

INTRAGASTRIC ACIDITY

The results of the three treatments are shown in Figure 1 (median pH curves) and the Table (median pH values plus interquartile range for the different time periods). Both treatments with ranitidine led to a significant increase of intragastric mean and median pH compared with placebo ($p < 0.0002$). The difference between the two ranitidine treatments was statistically significant ($p < 0.004$).

The total number of highly acidic electrode readings ($\text{pH} < 1.5$) over a 24 h period was reduced significantly with the administration of the drug at 1800 h compared to the bedtime or placebo treatment ($p < 0.012$ or $p < 0.0002$, respectively).

PLASMA RANITIDINE CONCENTRATIONS

The plasma ranitidine concentrations correlated well with the time of administration of the drug. On placebo, plasma concentrations were undetectable by radioimmunoassay. The area under the curve was 2704+749 (mean+SD) on ranitidine at 2200 hours and 3886+711 on ranitidine at 1800 hours ($p < 0.01$).

Peak plasma concentrations were 416+118 ng/ml (mean+SD) on ranitidine at 2200 hours and 613+124 ng/ml on ranitidine at 1800 hours ($p < 0.01$).

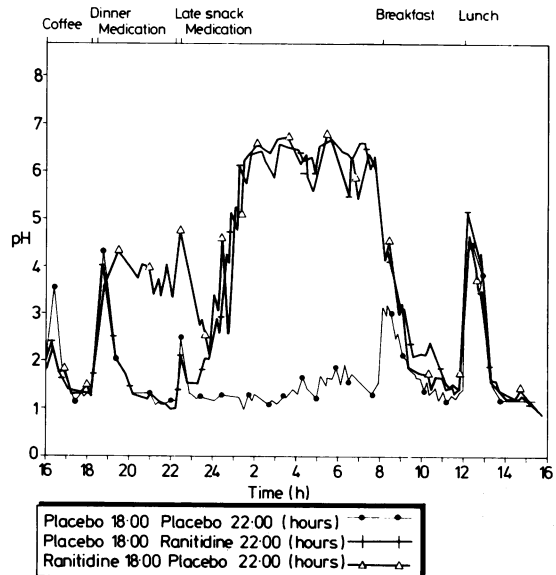


Fig. 1 Median pH-curves after administration of (a) placebo at 1800 h and 2200 h (b) placebo at 1800 h and 300 mg of ranitidine at 2200 h (c) 300 mg of ranitidine at 1800 h and placebo at 2200 h ($n=12$).

Table Median pH values and interquartile range for different time periods after oral administration of 300 mg ranitidine or placebo at 1800 h and 2200 h (n=12).

drug administration		period		1600–1600	1800–2200	2200–0600	0600–1600						
		1800	2200										
Placebo	Placebo	1.4	1.45	1.7	1.2	1.45	2.2	1.1	1.15	1.6	1.5	1.55	1.9
	Ranitidine (300 mg)	2.0	2.55*	3.2	1.3	1.40▲	1.5	4.1	5.60●	6.3	1.9	2.60■	3.5
Ranitidine (300 mg)	Placebo	2.5	3.35*	3.8	3.1	3.70▲	4.3	4.5	5.55●	6.1	1.5	2.05■	2.4

* p<0.004; ▲ p<0.002; ● nonsignificant; ■ p<0.05.

Discussion

Although there has been much discussion of single nocturnal dosing with H2-receptor antagonists and the importance of nocturnal gastric acidity in the context of duodenal ulcer disease, the optimal time of administration of antisecretory drugs is still controversial. Thus, recommended drug intake in recently published pharmacological and clinical studies has varied from 1800 h to 2200 h^{1,6,14,15} or even later (drug before sleep).^{2,3}

In a previous study using 24 h intragastric pH-metry, we were able to show that patients with active duodenal ulcers show high concentrations of acidity from early evening to early morning.⁴ We speculated

that nocturnal acidity could be controlled better with administration of antisecretory drugs after dinner (1800 h).

The present study clearly shows that the early evening dose of ranitidine is superior to bedtime administration in reducing median 24 h intragastric acidity.

The percentage of highly acidic electrode readings over the whole 24 h period was reduced significantly with administration of the drug at 1800 h compared with 2200 h (p<0.012).

A possible explanation for the improved efficacy of the early drug intake is shown in Figures 2 and 3. After dinner, when stimuli to acid secretion are high, oral administration of ranitidine results in high

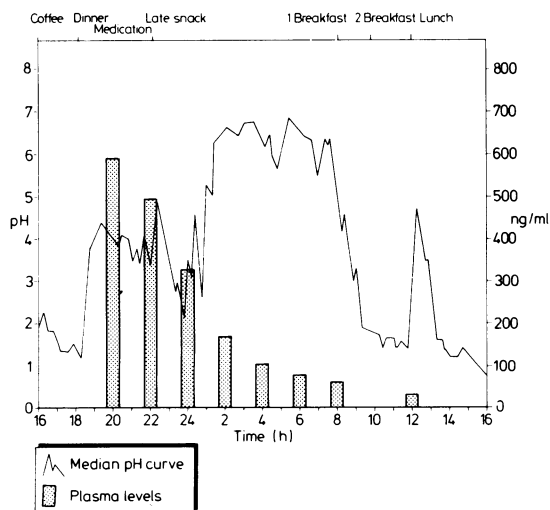


Fig. 2 Ranitidine plasma levels (NG/ML) and median pH-curve after administration of 300 mg ranitidine at 1800 h (n=12).

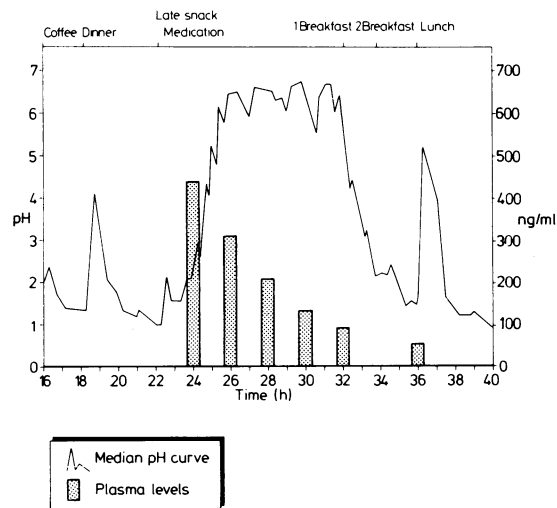


Fig. 3 Ranitidine plasma levels (NG/ML) and median pH-curve after administration of 300 mg ranitidine at 2200 h (n=12).

plasma ranitidine concentrations and a strong suppression of acidity before 2400 hours. After midnight, when stimuli to gastric acid secretion are low, both treatments lead to an equal and nearly total suppression of acidity, independent of whether blood levels are high or low. In the following early morning, the inhibitory effect of the H₂ receptor antagonist is surmounted by the meal stimulus of the breakfast in both treatment groups and the expected advantage of acid inhibition due to the later administration is small.

As both the area under curve and peak plasma concentrations of ranitidine are higher after the early administration of the drug, the improved inhibition of acid secretion may be related not only to the time of drug intake, but also to a more efficient absorption of the H₂ antagonists from a full rather than from an empty intestinal tract. As other investigators have obtained contrary results on the latter observation,¹⁶ further studies on ranitidine pharmacokinetics are required.

As reduction of intragastric acidity is an important therapeutic effect of H₂ antagonists, the present results suggest that healing rates of duodenal ulcers should improve with administration of the drug in the early evening. If these results in normal volunteers with ranitidine at 1800 h are also found in patients with duodenal ulcer, then this dose timing should be evaluated in a clinical trial.

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