Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer

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SUMMARY Twenty-four hour intragastric acidity and nocturnal acid secretion were measured in 10 males with duodenal ulcer in four separate 24 hour studies, during which the subjects ate normal meals, had unrestricted physical activity, and consumed their customary quantities of tobacco. The medication consisted of either placebo, or cimetidine 200 mg tds and 400 mg at night, or ranitidine 150 mg bd, or 200 mg bd. Ranitidine 150 mg bd decreased mean 24 hour hydrogen ion activity from 41·8 mmol/l to 13·1 mmol/l (−69%, p < 0·001) and nocturnal acid output from 6·1 mmol/h to 0·6 mmol/h (−90%, p < 0·01). This degree of inhibition was significantly greater than that due to cimetidine (p < 0·01 for 24 hours acidity, < 0·05 for night time acid output). Plasma concentrations of ranitidine were greater than the IC₂₀ for more than eight hours after the 150 mg dose. Ranitidine 200 mg conferred no additional advantage. Ranitidine 150 mg bd should be tested in therapeutic trials.

Ranitidine is a new specific histamine H₂-receptor antagonist which differs chemically from other histamine H₂ blockers in having a furan, rather than an imidazole or thiazole, ring structure.¹² (Fig. 1). Comparisons with cimetidine have shown ranitidine to be four to 10 times more potent on a molar basis, the ratio depending on the test system used.³-⁶ The dose of ranitidine needed for ulcer healing has not been determined experimentally. It was decided to compare the effects of twice daily regimens of ranitidine 150 mg and 200 mg with the standard dose of cimetidine (1 g per day) and placebo on intragastric acidity and nocturnal acid output in patients with duodenal ulcer.

Methods

PATIENTS
Ten male patients with endoscopically proven chronic duodenal ulcers in remission were studied. The mean age of the patients was 30 years (range 21–40 years), average weight 77 kg (range 65–88 kg) and they smoked an average of 14 cigarettes daily (range 0–25 cigarettes). Five were receiving maintenance cimetidine 400 mg at night, but all medication was stopped five days before the start of each phase of the experiment. All the subjects gave their informed consent to the study, which was approved by the appropriate ethical committees.

Each patient was studied on four separate occasions not less than one week apart. The experimental design is summarised in Fig. 2.

PROCEDURE
The experimental, dietary, and environmental conditions were identical for all subjects on each study day. The 24 hour experimental method has been described previously.⁴ All patients were admitted to a specially designated medical ward on the evening
Fig. 2  Plan for 24 hour experiment. Drugs administered at the times indicated by the arrows above the time line. Blood samples taken at the times indicated by the arrows below the time line. The dark squares represent standard meals. pH of gastric contents was measured at each hour from 0800. Overnight acid output was measured during the times shown.

Fig. 3  Mean hourly $H^+$ activity throughout the experimental period. Dark squares on horizontal axis represent standard meals. The hatched area represents the placebo result. The stars at the bottom of the Figure represent the times when the inhibition of $H^+$ caused by ranitidine is significantly greater than that by cimetidine.

Fig. 4  Mean hourly $H^+$ activity throughout the experimental period. The hatched area represents the placebo result. One standard error is shown at all points.
Comparison of the effects of ranitidine, cimetidine and placebo

before the study day and were intubated with a 10 FG Salem Sump nasogastric tube. Throughout the experiment the patients were encouraged to remain ambulant within the ward. The menu (breakfast, mid-morning drink, lunch, tea, supper, and night-cap) was identical during the four studies. Throughout the first experiment the patients kept a careful log of fluid and cigarette consumption and were required to follow the established pattern exactly during each of the three subsequent studies.

Starting at 0800 h on the morning of each study day, a 5–10 ml sample of gastric contents was aspirated at one hour intervals using syringe suction. The pH of the samples was measured immediately to the nearest 0-01 pH unit with a glass electrode and pH meter (Radiometer, Copenhagen). The calibration of the electrode was checked before each batch of measurements using standard buffers (pH 4.0 and 7.0).

Overnight (between 0100 and 0700 h) gastric secretion was aspirated continuously by pump suction supplemented when necessary by manual suction. The aspirated juice was pooled in one hour collections and aliquots were titrated with 0-1 M NaOH to pH 7-0 using an automatic titrator and burette (Radiometer, Copenhagen). The results were expressed in terms of mean hourly H+ activity for the hourly sampling observations and in mean hourly nocturnal acid output for the continuously aspirated nocturnal samples.

The drugs studied were administered orally in tablet form after meals at the times indicated in Fig. 2. Every patient received each of the following drugs on one of the four separate occasions: cimetidine 1 g per day; ranitidine 150 mg bd; ranitidine 200 mg bd; or placebo. The medication to be tested was started 24 hours before the study days, in order to reproduce conditions approximating to those of clinical therapy. Venous blood was sampled for plasma ranitidine concentrations via an indwelling

Table 1  Mean values of 24 hour intragastric acidity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean 24h H⁺ activity (mmol/l) (± SEM)</th>
<th>Percentage fall in H⁺ activity</th>
<th>Mean Intragastric pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>41.8 ± 1.5</td>
<td>—</td>
<td>1.38</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>21.6 ± 1.2*</td>
<td>48</td>
<td>1.67</td>
</tr>
<tr>
<td>150 mg bd</td>
<td>13.1 ± 1.0†</td>
<td>69</td>
<td>1.88</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>12.1 ± 1.1†</td>
<td>71</td>
<td>1.92</td>
</tr>
<tr>
<td>200 mg bd</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* P < 0.001 compared with placebo. † P < 0.001 compared with placebo and cimetidine.

Fig. 5  Overnight acid output. Hourly mean values ± one standard error.
'butterfly' cannula kept patent with heparinised saline. Plasma ranitidine concentration was measured by high pressure GLC.

Statistical comparisons were made using the paired Student's t test or the chi2 test.

Results

All patients tolerated well the procedures associated with the study and no unwanted effects were reported. There were no abnormalities in the laboratory profiles.

24 hour intragastric acidity

The results of the four regimens on 24 hour intragastric acidity are shown in Figs. 3 and 4; the mean values are in Table 1. The mean intragastric H+ activity in the 10 duodenal ulcer patients was 41.8 ± 1.5 mmol/l (SEM) in the control studies with placebo; it was significantly (p < 0.001) lowered by cimetidine 1 g daily to 21.6 ± 1.2 mmol/l. Both these results differ significantly (p < 0.001) from those recorded when ranitidine was used. H+ activity was additionally reduced by ranitidine 150 mg bd to 13.1 ± 1.0 mmol/l and 12.1 ± 1.1 mmol/l by ranitidine 200 mg bd. There was no significant difference between the inhibition achieved with the two doses of ranitidine.

Nocturnal acid secretion

The effect of the four medications tested on the overnight acid output is shown in Fig. 5. Both the H2 receptor antagonists markedly inhibited mean hourly nocturnal output. Compared with placebo, the nocturnal acid secretion was diminished by cimetidine from 6.1 ± 0.7 mm/h to 1.8 ± 0.4 mmol/h (p < 0.01, 70% inhibition). Ranitidine 150 mg bd produced 90% inhibition to 0.6 ± 0.1 mmol/h (p < 0.01) and ranitidine 200 mg bd produced 89% inhibition to 0.7 ± 0.2 mmol/h (p < 0.01). The suppression of acid secretion by ranitidine was significantly greater (p < 0.05) than that caused by cimetidine, but the higher dose of ranitidine was not different from the lower. The number of samples aspirated between 0100 and 0700 h with a pH > 5.0 is shown in Table 2.

Absorption of ranitidine

The concentration of ranitidine in the peripheral venous blood of seven patients during the studies is shown in Fig. 6. The initial values are different from zero because the medication was started 24 hours before the study days. These measurements show concentrations of ranitidine above the IC50 level for at least eight hours after the 150 mg dose. The mean plasma ranitidine level 12 hours after the

Table 2 Mean values of nocturnal acid output (0100–0700h)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean nocturnal acid output (mmol h⁻¹)</th>
<th>Percentage fall in acid output</th>
<th>Percentage of samples with pH &gt; 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>1.3†</td>
<td>70</td>
<td>39†</td>
</tr>
<tr>
<td>150 mg bd</td>
<td>0.7†</td>
<td>89</td>
<td>53†</td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.01 compared with placebo.
† p < 0.01 compared with placebo and p < 0.05 compared with cimetidine.
‡ p < 0.001 compared with placebo (by χ² analysis).

Fig. 6 The points plotted represent the mean results from seven patients as three were not sampled. The IC50 is approximately 100 ng/ml.
evening dose was 76 ± 9.6 ng/ml (± SEM) (150 mg dose) and 88 ± 8.6 ng/ml (± SEM) (200 mg dose).

Discussion

It has been suggested that histamine H₂ receptor blockade is dependent upon the presence of an imidazole ring in any potential antagonist. However, ranitidine has been shown to be a specific histamine H₂-receptor antagonist despite the substitution of the imidazole by a furan ring. The pharmacological activity of ranitidine has been tested in man in a number of ways, including observations on the effect on maximal gastric acid secretion stimulated by histamine, pentagastrin, and food, and on nocturnal acid secretion. We have tested the pharmacological effect of ranitidine in response to more physiological stimuli. The method used in this study has been validated previously and has been shown to be a useful technique in the study of anti-secretory drugs.

The two doses of ranitidine used in this study were selected for two reasons. Firstly, we tested the possibility that a twice-daily dosage regimen would decrease intragastric acidity and nocturnal acid secretion to a similar extent as cimetidine in standard dosage. It was also pertinent to show whether plasma concentrations of ranitidine at, or above, the IC₅₀ level could be maintained for a reasonable period after twice daily administration of the drug. Preliminary data from volunteer studies suggested that this was possible with a 178 mg dose of ranitidine (Richards et al., personal communication) and this was used as the basis for choosing the dosage regimen. Secondly, other studies have shown that ranitidine is more active than cimetidine, but the molar potency ratio varies quite widely, according to the test system employed (Table 3). In this experiment the molar ratio of cimetidine to ranitidine used is 4:2:1.

Our observations show that ranitidine 150 mg twice daily inhibits mean 24 hour intragastric acidity by 70%. Nocturnal acid output decreased by 90% and both aspects of acid secretion were significantly lower when compared in the same patients with cimetidine in standard dosage. Detailed analysis of the 24 hour intragastric acidity data (Figs. 3 and 4) shows that the most marked differences occurred during the morning and, to a lesser extent, at night. In our experience it is difficult to achieve substantial inhibition of intragastric acidity during the early evening (1600–1900 h) with either drug. This phenomenon has been observed in other experiments. It is surprising that both H₂-receptor antagonists seem less effective at this time of day and the reasons for this are not clear.

Increasing the daily dose of ranitidine from 300–400 mg achieved only a marginal additional reduction in H⁺ activity despite measurably higher concentrations of the drug in the plasma (Fig. 6). This observation is similar to that which we previously reported with cimetidine, when doubling the dose from 800–1600 mg daily conferred no additional advantage in terms of day-time acidity. In contrast with observations with ranitidine, however, increasing the night-time dose of cimetidine caused greater inhibition of nocturnal acid secretion. In other studies, increasing the dose of cimetidine from 1.2–2.4 g produces significantly more inhibition during the day but not at night. It may be that after the evening dose of ranitidine 150 mg, H₂-receptor site occupancy by the drug is at its maximum and additional inhibition of acid output is not possible. It may be that ranitidine 150 mg is acting at the top end of the dose response curve for the drug and therefore only large changes in dosage will increase the inhibitory response. In the period between 0500 and 0800 h the measured effect of cimetidine was decreasing, while ranitidine continued to have substantial antisecretory activity. This raises the question whether ranitidine is longer acting than cimetidine. Additional experiments to clarify this point are indicated.

The mean 24 hour intragastric pH levels were higher than those recorded with cimetidine, but remained below 2.00. The relatively low intragastric pH during treatment with ranitidine should allow accelerated healing of duodenal ulcers, as similar values have been recorded with cimetidine. Comparison of the present results with earlier 24 hour studies from our previous experiments shows that the inhibition of nocturnal acid secretion due to cimetidine is similar. The overall 24 hour response of the intragastric acidity was less marked in this study (48%) than in earlier experiments (70%) in normal subjects and 63% in patients with duodenal...
ulcer. However, mean inhibition of 24 hour intragastric $H^+$ activity in 31 duodenal ulcer patients we have studied is 56%. 14 The reasons for these differences are difficult to define precisely, but may be due to varying responsiveness of different groups of patients to the drug. The subjects in this study had all received cimetidine previously and five were receiving maintenance therapy. However, all medication was stopped five days before each test. The elimination half life of cimetidine is approximately two hours and acid secretory responses have been reported to be normal within five days of stopping treatment, even after prolonged exposure to cimetidine. 15, 16 The five subjects who had been on cimetidine maintenance showed similar pharmacological responses to both drugs as the remainder of the group.

Our data suggest that, under the conditions of this experimental technique which approximate to everyday life, ranitidine is more than four times as potent as cimetidine on a molar basis in decreasing intragastric acidity. The degree of acid inhibition comparable with that produced during treatment with four daily doses of cimetidine was, in this study, produced by a twice daily dose of ranitidine. The data also suggest that increasing the dose of ranitidine from 150–200 mg twice daily will not result in additional suppression of intragastric acidity or nocturnal acid output. Twice daily medication has clear advantages in terms of patients’ compliance and convenience. On the basis of this study we consider that the dose of ranitidine 150 mg bd can be recommended for clinical evaluation in the treatment of peptic and related disorders.

We are very grateful to all the nursing and ancillary staff at the Royal Naval Hospital, Haslar, without whose help and co-operation this study could not have been performed. We also thank Dr D A Richards (Glaxo Allenby Research) for the supplies of ranitidine and for the facility to measure plasma levels. Our thanks are also due to Ms P Evans and Miss P Simpson for secretarial help, and to Mr J Etherington for photography.

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