Effect of bedtime ranitidine on overnight gastric acid output and intragastric pH: dose/response study and comparison with cimetidine

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SUMMARY A dose/response study has been carried out in seven patients with endoscopically proven duodenal ulcers in symptomatic remission, measuring intragastric pH and gastric acid output overnight after a bedtime dose of ranitidine (75 mg, 150 mg, and 300 mg); and the results have been compared with placebo and with bedtime cimetidine 400 mg. The currently recommended ranitidine maintenance dose (150 mg) was the optimum because it was significantly more effective than ranitidine 75 mg in terms of intragastric pH but not of acid output, and there was no difference from 300 mg in terms of either measurement. It was also significantly more effective than the currently recommended cimetidine maintenance dose (400 mg) in terms of inhibiting overnight acid output (92% vs 80% inhibition, $p < 0.05$), and of maintaining intragastric pH above 5 (100% vs 17% of the overnight period, $p < 0.001$).

The mainstay of maintenance therapy for duodenal ulcer has for several years been a single bedtime dose of either cimetidine or, more recently, ranitidine. Nocturnal acid hypersecretion is widely regarded as the single most important factor in the pathogenesis of duodenal ulcer,¹⁻³ and can be markedly suppressed by a single bedtime dose of an H_2 receptor antagonist.⁴ An inadequate reduction in nocturnal hydrogen ion activity on treatment correlates with a poor clinical response in terms of endoscopic healing.⁵ Despite these facts, daytime doses have until recently been given for the initial treatment of duodenal ulcer. Ireland and colleagues⁶ have now shown that duodenal ulcer healing can be achieved with equal efficacy using ranitidine 300 mg at bedtime or 150 mg twice daily, and Delattre and Dickson⁷ and Lacerte and colleagues⁷ have found no significant difference for duodenal ulcer healing using cimetidine in doses of 800 mg at bedtime or 400 mg twice daily. On the other hand, Capurso and colleagues⁸ found cimetidine 800 mg at bedtime superior to cimetidine 400 mg

twice daily in endoscopically assessed healing of duodenal ulcer.

The stimulus to check whether a single bedtime dose of an H_2 receptor antagonist was as effective as a twice daily dose came from the earlier finding by Gledhill and colleagues⁴ that the reduction in mean 24 hour intragastric hydrogen ion activity was no less for ranitidine 300 mg at bedtime than for 150 mg twice daily, and for cimetidine 800 mg at bedtime than for 400 mg twice daily.

It has now become important to determine the optimal bedtime regimen for initial treatment of duodenal ulcer as well as for long term maintenance. The optimum dose for cimetidine and ranitidine is not clear, nor is it clear which is the more effective drug in ulcer healing. We have already published a dose/response study for bedtime cimetidine,⁹ which showed in six patients with endoscopically diagnosed duodenal ulcer that bedtime cimetidine 400 mg had the optimum effect on overnight gastric acid output, being significantly more effective than 200 mg and no different in effect from 800 mg. Similar studies by Longstreth¹⁰ and Broor¹¹ have agreed with us in showing a greater effect for cimetidine 400 mg than for 200 mg, although Gledhill and colleagues⁴ have reported that cimetidine 800 mg at bedtime has a

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greater effect on overnight acid output than 400 mg twice daily.

In the present study we have carried out a dose/response study for ranitidine, following the same experimental design as before.⁹ We have compared bedtime ranitidine (75 mg, 150 mg and 300 mg) with bedtime cimetidine 400 mg. We chose this dose of cimetidine because it is the recommended dose for maintenance therapy; it had also shown the optimum effect on overnight acid output in our previous study. We also report intragastric pH data from the earlier cimetidine study for comparison with the ranitidine data, because these data have not been published previously. The aim has been to determine the optimum bedtime dose of a currently available histamine H₂ receptor antagonist in terms of gastric acid output and in terms of intragastric pH.

Methods

SUBJECTS

Seven male volunteers were studied (aged 26–68 years, mean 45 years). All had duodenal ulcers confirmed by endoscopy, but were asymptomatic on no treatment at the time of the study. Only one subject (subject 7) was a smoker (20 cigarettes/day) at the time of the study, and two subjects had been smokers in the past (subjects 3 and 4). Subjects 5 and 7 failed to heal their ulcers during cimetidine treatment (1 g daily for 12 weeks). These two subjects, together with subject 1, were treated subsequently by surgery. The study was approved by the local hospital ethical committee and all subjects gave written informed consent.

EXPERIMENTAL DESIGN

For each night time study the subjects were admitted to hospital in the evening after work and returned to their usual employment the following day. At 6 00 pm they ate the same standard hospital meal on each occasion (one chicken breast plus salad). They remained dressed and ambulant. None smoked on the ward. The same pattern of evening activities was repeated for each admission. At 9 30 pm a size 16 ch Ryle/Levin nasogastric tube was passed. On the first night this was positioned radiologically in the most dependent part of the stomach. On subsequent nights the same length of tube was passed and the position checked by a water recovery test.¹² At 10 00 pm the trial tablets were administered with 50 ml water and nitrazepam 10 mg. Night sedation was used to prevent normal sleep patterns being disturbed by either the repeated gastric aspirations or the background ward noise. The patients then lay on their right side for one and a half hours to facilitate gastric emptying. At 12 30 am they assumed the left lateral

position and were maintained in this position for the duration of the study. The stomach was emptied by manual aspiration and a sample preserved for estimation of cimetidine or ranitidine content. Gastric contents were then aspirated continuously for six hours using a suction pump (–4 cm H₂O). Suction was interrupted manually every 15 minutes to prevent blockage.

Gastric samples were collected in hourly aliquots, and stored at –20°C for subsequent analysis by someone unaware of the treatment given. pH was measured by Radiometer electrode. Titration was carried out using 0.1 N NaOH to endpoints of pH 7 and 9.5 according to a pH meter (Radiometer electrode). pH 7 was chosen being the neutral point, and pH 9.5 because many samples were well above pH 7 and therefore an end point of only 7 would have reduced the sensitivity of our acid output measurements, and further because it coincided approximately with the phenolphthalein endpoint used in our previous study. For both experiments the pH meter was standardised using buffer solutions of pH 4 and 7. Patients were given on five separate nights one week apart the following different drug regimens: placebo, ranitidine 75 mg, 150 mg, and 300 mg, and cimetidine 400 mg. The order was randomised. The trial was double blind in the sense that neither the patient, nor the person carrying out the laboratory analyses, were aware of the treatment given.

Acid output was calculated using pH 9.5 as endpoint. For presentation of the acid output data, mean nocturnal acid output at each dose was calculated, and also percentage inhibition compared with the placebo output. For the presentation of intragastric pH results, mean and median percentage of hours was calculated during which the intragastric pH remained above each pH unit and the median values have been given. The overnight acid output on different regimens was compared by analysis of variance and by multiple comparisons of means with the Newman-Keuls procedure. A logarithmic transformation was used to obtain a normal distribution. In comparing different regimens for the proportion of pH readings above 5, a linear logistic model was fitted by maximum likelihood using GLIM, the Royal Statistical Society program. For all these analyses a simple randomised block model was used. As measurements were made at intervals of at least seven days, there was no possibility of carry over effects between treatments and so the order of treatment was ignored. The proportion of pH readings above 5 was chosen because pepsin activity rapidly falls above this level.¹³ pH was also expressed in terms of median plus 30th and 70th percentiles. These are the only percentiles that can easily be calculated in the present group of seven and the previous group of six patients.

Table Mean nocturnal acid output (mmol/h) on each drug regimen (percentage inhibition compared with placebo is in brackets)

Patient	Placebo	Cimetidine 400 mg	Ranitidine 75 mg	Ranitidine 150 mg	Ranitidine 300 mg
1	2.48	1.37 (45%)	0.28 (89%)	1.34 (46%)	0.70 (72%)
2	5.74	0.94 (84%)	0.27 (95%)	0.28 (95%)	0.10 (98%)
3	11.50	0.28 (98%)	0.77 (93%)	0.18 (98%)	0.29 (97%)
4	2.95	0.26 (91%)	0.26 (91%)	0.18 (94%)	0.32 (89%)
5	5.87	4.25 (28%)	1.14 (81%)	0.61 (90%)	0.63 (89%)
6	5.54	1.60 (71%)	1.40 (75%)	0.49 (91%)	0.55 (90%)
7	2.93	0.95 (68%)	0.44 (85%)	0.39 (87%)	0.34 (88%)
Geometric mean	4.63	0.93	0.52	0.39	0.36
Percentage inhibition		80%	89%	92%	92%
95% confidence limits		60%–90%	78%–94%	83%–96%	85%–96%

Results

GASTRIC RECOVERY OF CIMETIDINE AND RANITIDINE

The mass of drug aspirated was expressed as the percentage of the doses given. For cimetidine this was between 0.002% and 3.3% (mean 0.9%) and for ranitidine 0–0.79% (mean 0.12%) if one subject was omitted whose recovery was 25% after ranitidine 150 mg. The figures for overnight acid output and intragastric pH were no different in this one subject from those in the rest of the subjects. This subject with 25% recovery of ranitidine on a dose of 150 mg at bedtime had a recovery of only 0.03% on ranitidine 75 mg and 0.02% on ranitidine 300 mg.

PERCENTAGE INHIBITION OF NOCTURNAL GASTRIC ACID OUTPUT

The results are shown in the Table. Ranitidine 75 mg caused an inhibition in acid output of 89%, ranitidine 150 mg an inhibition of 92% and ranitidine 300 mg an inhibition of 92%. No significant difference was found between results for all three doses of ranitidine. The percentage inhibition for cimetidine 400 mg (80%) was significantly less than for ranitidine 150 mg ($p < 0.05$) and for ranitidine 300 mg ($p < 0.01$).

INTRAGASTRIC pH

The results are shown in Figure 1 (mean pH). For cimetidine 400 mg, median (*not* mean) pH rose above 5 in 17% of the samples, compared with 0% on placebo. On ranitidine 75 mg pH rose above 5 for 33% of the samples, a higher proportion than on cimetidine 400 mg ($p < 0.05$), but less than on ranitidine 150 mg (100%, $p < 0.05$) or on ranitidine 300 mg (100%, $p < 0.001$).

Figure 2 shows median values for each hourly pH for the seven subjects, and the 30th percentile. The 70th percentile is not shown, in the interest of clarity. In the case of ranitidine 75 mg and cimetidine 400 mg, the 70th percentile is further from the median value

than is the 30th percentile, because the values are skewed towards low pH values. In the case of the other three regimens (placebo, ranitidine 150 mg and 300 mg), the 70th percentile is a similar distance from the median value as the 30th percentile.

Discussion

In this study the ranitidine dose currently recommended for maintenance treatment (150 mg) was compared with other doses of ranitidine (75 mg and 300 mg) and with the cimetidine dose recommended for maintenance treatment (400 mg), which was also the optimum dose in terms of acid output determined in our previous study.⁹ Ranitidine 150 mg had a significantly greater effect in inhibiting acid output than cimetidine 400 mg. There was, however, no significant difference between any of the doses of ranitidine on the basis of acid inhibition. All active treatments were significantly better than placebo. Although we are unaware of any data indicating whether or not night sedation influences acid secretion, it should not in any case have affected the comparison between the different regimens, as all patients received the same dose of nitrazepam on each regimen.

Hunt and colleagues¹⁴ have recently shown from an examination of the literature that ulcer healing on H_2 receptor antagonists correlates well with suppression of nocturnal H^+ activity but not with nocturnal acid output. Although they did not relate prevention of relapse to these measurements, it might be predicted that the pH of the fluid bathing the duodenum overnight would be more important than the total amount of acid flowing through the duodenum in influencing ulcer relapse as well as ulcer healing. In view of these findings, we have re-analysed the data from our previous study⁹ in terms of intragastric pH as well as acid output (Figs 3, 4). Whereas measurements of acid output showed no difference between

Fig. 1 Mean percentage of gastric samples having a pH above each pH unit after bedtime ranitidine (75 mg, 150 mg, and 300 mg), cimetidine (400 mg) and placebo.

bedtime cimetidine 400 mg and 800 mg, measurements of intragastric pH showed that with cimetidine 800 mg the pH remained above 5 for a significantly greater period of time than with cimetidine 400 mg. Figure 3 shows that this effect was consistent at other pH levels as well. In the present study, this method of analysis showed no significant difference between ranitidine 150 and 300 mg, although these doses were significantly more effective than ranitidine 75 mg. The intragastric pH results were in agreement with the acid output results in confirming that ranitidine

was more effective than cimetidine at the recommended doses for maintenance treatment (ranitidine 150 mg and cimetidine 400 mg).

A problem with comparisons between different studies is that duodenal ulcer patients do not represent a homogeneous group. Hunt⁸ has described two separate groups of patients, whom he has termed responders and non-responders according to their pH response six hours after a bedtime dose of cimetidine. In his study these two groups were widely separated, whereas in our study we found wide differences but a continuous spectrum with no separation into two distinct populations. The subjects in our two studies differed in responsiveness, because the subjects in the first study⁹ had an intragastric pH more than 5 for 59% of the time (median) compared with 17% of the time in the present study in response to cimetidine 400 mg at bedtime. The subjects participating in the study of Gledhill and colleagues¹ were also much less responsive than the subjects in our first study, as the arithmetic mean reduction in acid output in response to cimetidine 400 mg at bedtime was only 69% compared with a response to one dose of 400 mg cimetidine at bedtime of 93% in our previous study and 95% in the study of Longstreth and colleagues.¹⁰ Our methodology was the same as for all the other studies quoted in this publication in that it involved removal of all the gastric contents every hour in order to measure hourly acid output. This may have introduced an artefact in the analysis of intragastric pH since our measurement only referred to the pH of the fluid secreted during the preceding hour, thus obviating

Fig. 2 pH, median and 30th percentile, for successive hours after bedtime ranitidine (75 mg, 150 mg, and 300 mg), cimetidine (400 mg) and placebo. The bedtime doses were given at 10 pm, the first hourly gastric aspirate was taken from 12.30 am to 1.30 am (labelled 3 hours in the figure) and the last sample was taken from 5.30 to 6.30 am (labelled 8 hour sample in the Figure).

Fig. 3 Mean percentage of gastric samples having a pH above each pH unit after bedtime cimetidine (200 mg, 400 mg, 800 mg) and placebo.

any cumulative effect on intragastric pH from fluid secreted during previous hours and not yet emptied from the stomach. As all our comparisons of intragastric pH are within - patient comparisons of different drug regimens, this consideration should not affect the validity of these comparisons.

Our data on both acid output and pH suggest that the recommended dose for ulcer healing (300 mg) may be unnecessarily high, although this conclusion must be cautious in view of the small patient numbers involved. Our data on pH support the currently recommended bedtime dose of ranitidine for main-

tenance therapy (150 mg), although the data on acid output suggest that a lower dose may be optimal. Further endoscopically controlled clinical trials are necessary to give a definitive answer as to what is the optimum bedtime regimen for H_2 blockers for ulcer healing and for prevention of relapse. Our data for both sets of measurements suggest that in their currently recommended doses for bedtime maintenance therapy, ranitidine (150 mg) is more effective than cimetidine (400 mg), and this finding has been confirmed in large controlled trials.^{15 16}

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