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

J B CHAMBERS, D PRYCE, J M BLAND, AND T C NORTHFIELD

From the Norman Tanner Gastroenterology Unit, St James' Hospital and Department of Medicine II, St George's Hospital Medical School, London

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, and can be markedly suppressed by a single bedtime dose of an H2 receptor antagonist. An inadequate reduction in nocturnal hydrogen ion activity on treatment correlates with a poor clinical response in terms of endoscopic healing. Despite these facts, daytime doses have until recently been given for the initial treatment of duodenal ulcer. Ireland and colleagues 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 Dickson and Lacerte and colleagues 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 colleagues 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 H2 receptor antagonist was as effective as a twice daily dose came from the earlier finding by Gledhill and colleagues 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, 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 Longstreth and Broor have agreed with us in showing a greater effect for cimetidine 400 mg than for 200 mg, although Gledhill and colleagues have reported that cimetidine 800 mg at bedtime has a
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. 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 treat-
ment (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 600 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 930 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. At 1000 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 back-
ground 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 estima-
tion 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 pre-
vent 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 measure-
ments, and further because it coincided approxi-
ately 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 end-
point. 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 dif-
ferent regimens was compared by analysis of variance
and by multiple comparisons of means with the New-
man-Keuls procedure. A logarithmic transformation
was used to obtain a normal distribution. In compar-
ing different regimens for the proportion of pH read-
ings above 5, a linear logistic model was fitted by
maximum likelihood using GLIM, the Royal Statis-
tical 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 treat-
ments and so the order of treatment was ignored. The
proportion of pH readings above 5 was chosen
because peptic 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)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo</th>
<th>Cimetidine 400 mg</th>
<th>Ranitidine 75 mg</th>
<th>Ranitidine 150 mg</th>
<th>Ranitidine 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.48</td>
<td>1.37 (45%)</td>
<td>0.28 (89%)</td>
<td>1.34 (46%)</td>
<td>0.70 (72%)</td>
</tr>
<tr>
<td>2</td>
<td>5.74</td>
<td>0.94 (84%)</td>
<td>0.27 (95%)</td>
<td>0.28 (95%)</td>
<td>0.10 (98%)</td>
</tr>
<tr>
<td>3</td>
<td>11.50</td>
<td>0.28 (98%)</td>
<td>0.77 (93%)</td>
<td>0.18 (98%)</td>
<td>0.29 (97%)</td>
</tr>
<tr>
<td>4</td>
<td>2.95</td>
<td>0.26 (91%)</td>
<td>0.26 (91%)</td>
<td>0.18 (94%)</td>
<td>0.32 (89%)</td>
</tr>
<tr>
<td>5</td>
<td>5.87</td>
<td>4.25 (28%)</td>
<td>1.14 (81%)</td>
<td>0.61 (90%)</td>
<td>0.63 (89%)</td>
</tr>
<tr>
<td>6</td>
<td>5.54</td>
<td>1.60 (71%)</td>
<td>1.40 (75%)</td>
<td>0.49 (91%)</td>
<td>0.55 (90%)</td>
</tr>
<tr>
<td>7</td>
<td>2.93</td>
<td>0.95 (68%)</td>
<td>0.44 (65%)</td>
<td>0.39 (87%)</td>
<td>0.34 (88%)</td>
</tr>
</tbody>
</table>

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.2 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 H2 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 study1 in terms of intragastric pH as well as acid output (Figs 3, 4). Whereas measurements of acid output showed no difference between
Effect of bedtime ranitidine on overnight gastric acid output and intragastric pH

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. Hunt 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 study 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 colleagues 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. 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. 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.

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).
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 maintenance 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 H2 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

We thank Glaxo Group Research Limited for financial support and Mr Nigel James for technical assistance.

References

Effect of bedtime ranitidine on overnight gastric acid output and intragastric pH


