Maintenance treatment of duodenal ulceration: ranitidine 300 mg at night is better than 150 mg in cigarette smokers

F I Lee, M Hardman, M E Jaderberg

Abstract
Two hundred patients received either ranitidine 150 mg or 300 mg at night for 18 months to prevent duodenal ulcer relapse. Recurrence rates were lower in patients receiving the higher dose of ranitidine (3·1% v 9·7%, p=0·078, 6·5% v 16·7%, p=0·037; and 8·9% v 17·0%, p=0·121 at six, 12, and 18 months respectively). In patients receiving ranitidine 150 mg, recurrences were significantly more common in smokers than non-smokers after 12 and 18 months, while in patients receiving ranitidine 300 mg recurrence rates were similar in smokers and non-smokers. Ranitidine 300 mg at night abolishes the adverse effect of smoking observed during maintenance treatment with ranitidine 150 mg at night and may therefore be an appropriate maintenance dose for smokers who relapse during standard dose maintenance treatment.

Several drugs are effective in healing of duodenal ulcers but relapse occurs in up to 90% of patients during the following 12 months if treatment is stopped. Maintenance therapy is recommended in selected patients to reduce the likelihood of relapse and the associated morbidity and complications. Maintenance therapy with cimetidine 400 mg or ranitidine 150 mg provides one year ulcer-free intervals in 65–80% of patients. Nevertheless, patients who relapse on standard dose maintenance treatment pose a therapeutic problem. The present study was undertaken to determine whether maintenance treatment of duodenal ulcer with ranitidine 300 mg at night further reduces the incidence of recurrence compared with ranitidine 150 mg at night over an 18 month period.

Patients and methods
The study was a randomised double blind, single centre comparison of ranitidine 150 mg with ranitidine 300 mg at night administered for 18 months. Patients were entered into the study if they presented with dyspepsia or upper gastrointestinal bleeding, or both, and were shown to have one or more duodenal ulcers >5 mm in diameter which healed during four to eight weeks’ treatment with an H2 receptor antagonist. Patients with gastric ulceration, previous gastric surgery other than oversewing of a perforation, coincidental medical disease, or those who were receiving ulcerogenic drugs were excluded. The study was approved by the Ethics Committee of the Blackpool Fylde and Wyre Health Authority and all patients gave informed consent. Clinical assessment was carried out at two-monthly intervals. Endoscopic examinations were performed at six, 12, and 18 months and in those patients who developed symptoms suggestive of ulcer recurrence. Blood was withdrawn for standard haematological and biochemical safety checks at endoscopy visits.

STATISTICAL METHODS
Numbers of recurrences on each dose of ranitidine, and in smokers and non-smokers were compared using Fisher’s exact test. Cumulative recurrence rates were calculated using the product limit life table method. Patients who were withdrawn from the study for reasons other than ulcer relapses were included in analysis up to the time of the last valid endoscopic examination. Differences were deemed statistically significant if p was less than 0·05 for a two tailed test.

Results
Two hundred patients entered the study between April 1985 and April 1987. One hundred patients received ranitidine 150 mg at night and 100 received ranitidine 300 mg. Demographic features and ulcer history were similar in the two treatment groups (Table I). Twenty two patients (12 receiving ranitidine 150 mg) were withdrawn for reasons other than ulcer recurrence (Table II).

All other patients continued in the trial until either a recurrence had been detected or 18 months’ treatment had been completed.

ULCER RECURRENCE
Recurrent duodenal ulcers were detected in 23 patients (15 receiving ranitidine 150 mg). In no patient was recurrent ulceration associated with haemorrhage or perforation. Five of the recurrences (three in patients receiving ranitidine 150 mg) were considered as significant (Table I).

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**Table 1**: Features of the two treatment groups at entry to the trial

<table>
<thead>
<tr>
<th>Feature</th>
<th>150 mg ranitidine (n=100)</th>
<th>300 mg ranitidine (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>48·5 (13·6)</td>
<td>48·8 (13·6)</td>
</tr>
<tr>
<td>Sex M:F</td>
<td>68:32</td>
<td>65:35</td>
</tr>
<tr>
<td>Alcohol excess (&gt;6 units daily)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Smokers: non-smokers</td>
<td>66:34</td>
<td>63:37</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Previous</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>15</td>
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Department of Gastroenterology, Victoria Hospital, Blackpool
F I Lee
M Hardman
Glaxo Laboratories Limited, Greenford, Middlesex
M E Jaderberg
Correspondence to: Dr F I Lee, Department of Gastroenterology, Victoria Hospital, Blackpool, Lancashire.
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mg) were asymptomatic and detected at pre-
arranged endoscopic follow up. Cumulative
combined (symptomatic plus asymptomatic)
recurrence rates are given in Table III. Cumu-
lative symptomatic recurrence rates were 7-5%,
13-3%, and 13-6% in patients receiving ranitidine
150 mg and 2-1%, 4-0%, and 7-0% in patients
receiving ranitidine 300 mg at six, 12, and 18
months respectively.

EFFECT OF SMOKING ON ULCER RECURRENCE
In patients receiving ranitidine 150 mg at night,
ulcer recurrence was statistically significantly
more common in smokers than in non-smokers
after 12 and 18 months (Table IV and Figure). In
patients receiving ranitidine 300 mg at night,
however, recurrence rates were similar in smokers
and non-smokers throughout the period of
the study (Table IV and Figure). Thus,
increasing the maintenance dose of ranitidine to
300 mg at night abolished the adverse effect of
cigarette smoking that was observed during
maintenance with ranitidine 150 mg.

ADVERSE EVENTS
One patient in each treatment group experienced
diarrhoea, that was possibly attributable to
ranitidine and which resolved on stopping treat-
ment. Each patient subsequently received rani-
tidine for ulcer healing without recurrence of
diarrhoea. No changes in individual patients'
laboratory values occurred which were thought
to be caused by treatment. There were no
significant changes in population mean values
for any of the haematological or biochemical
indices during treatment with either dose or
ranitidine.

Discussion
Most duodenal ulcers recur within one year of
healing if treatment is stopped. Only one agent,
colloidal bismuth subcitrate, has been shown to
be followed by reduced relapse rates, but this
effect is relatively short term. Maintenance
treatment is generally recommended for particu-
lar groups of patients with duodenal ulceration,
for example those who have suffered previous
ulcer haemorrhage or recent perforation with
surgery limited to oversewing; elderly patients
or patients unfit for surgery; and patients receiving
anticoagulants, corticosteroids, or non-steroidal
anti-inflammatory drugs. Low dose maintenance
therapy with H2 receptor antagonists reduces the
annual cumulative recurrence rate to 20–30%. A
recent meta-analysis of duodenal ulcer main-
tenance therapy with ranitidine 150 mg or cime-
didine 400 mg at night concluded that cumulative
combined (symptomatic plus asymptomatic) one
year recurrence rates were 19% and 27% respect-
ively. The cumulative one year recurrence rate
observed during maintenance treatment with
ranitidine 150 mg at night in the present study
(17%) was thus similar to rates reported in the
medical reports.

A proportion of patients still relapse, how-
ever, on standard maintenance treatment and
full dose maintenance therapy has been recom-
mended for these. In the present study recur-
rence rates during treatment with ranitidine 300
mg at night were approximately half those during
treatment with ranitidine 150 mg. Two previ-
ously reported studies failed to show a therape-
utic benefit from increasing the standard
maintenance dose of cimetidine or famotidine in
duodenal ulcer disease. A multicentre com-

* Fisher's exact test p=0.04.
**p=0.02; tSmokers rates increasing common were mg)
18
24%
25%
23%
13%
Cumulative relapse rates
treatment

<table>
<thead>
<tr>
<th>Time (mths)</th>
<th>0-6</th>
<th>7-12</th>
<th>13-18</th>
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<tr>
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<td>93</td>
<td>96</td>
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<td>No 300 mg</td>
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<tr>
<td>95% CI</td>
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Comparison of cimetidine 400 mg with 800 mg showed that symptomatic recurrence rates during treatment with either dose of cimetidine were similar (17% and 15% respectively at one year) but that asymptomatic recurrences were more frequent in patients receiving the higher dose of cimetidine (10% and 16% respectively). Similarly, in a study comparing famotidine 20 mg with famotidine 40 mg, recurrence rates were 23% and 25% respectively after one year. A study comparing ranitidine 150 mg at night with ranitidine 150 mg twice daily in the maintenance of duodenal ulcer healing showed, however, that recurrence rates were reduced from 27% to 17% at one year by the higher dose of ranitidine. It has previously been reported that recurrence during maintenance treatment is more common in smokers than in non-smokers. This may relate to an adverse effect on plasma concentration of orally administered ranitidine in cigarette smokers. In the present study 83% of all recurrences were in smokers. The relative risk for ulcer recurrence was statistically significantly greater in smokers than in non-smokers receiving ranitidine 150 mg at night. In patients receiving ranitidine 300 mg at night, however, the recurrence rates were similar in smokers and non-smokers. This suggests that the reduction in recurrence rates during maintenance treatment with ranitidine 300 mg was attributable to a specific therapeutic benefit of the higher dose in cigarette smokers, although the possibility of a type I error cannot be entirely excluded. The results of the present study indicate that in patients who relapse during standard dose maintenance therapy and who are smokers (the majority), maintenance treatment with ranitidine 300 mg at night is an effective and safe therapeutic option to reduce the risk of further recurrence.

This work was presented at the American College of Gastroenterology in October 1989 (New Orleans).