Low dose maintenance treatment with cimetidine in duodenal ulcer: intermediate-term results

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Summary: Ulcer relapse rates during up to 2 years of prophylactic low-dose maintenance therapy (LDMT) with cimetidine 400 mg at bedtime was examined in 261 patients. Endoscopy was repeated every 6 months if asymptomatic, or whenever symptoms recurred. Relapse was defined as the recurrence of an ulcer crater or erosions or both.

In patients with non-refractory duodenal ulcer (those healed within 3 months) who comprise the majority, their likelihood of relapse at 6, 12, 18 and 24 months was: symptomatic 8%, 13%, 18%, 20%; silent 14%, 28%, 38%, 43%, respectively. In contrast, in patients with refractory ulcer, their symptomatic relapse rates were 36%, 45%, 46%, 48%, and silent 28%, 38%, 46%, 48% respectively. The outcome of a second course of LDMT was similar to the first. Narrowing the definition of relapse to exclude recurrence of erosions alone but without an ulcer decreased asymptomatic relapse in non-refractory ulcer patients by about half. No patient had any major side effects.

Thus, LDMT is a safe and effective way of keeping most patients with duodenal ulcer symptom free over 2 years.

Introduction

Low dose maintenance treatment (LDMT) with cimetidine at the standard dose of 400 mg at bedtime following healing of duodenal ulcer, markedly reduces the relapse rate over the next year (Burland et al., 1980; Misiewicz & Bradbury, 1984), but little is known of the outcome of longer periods of treatment. We therefore present our results of up to 2 years' follow-up. We have investigated the symptomatic and silent relapse rates and have observed that patients with a refractory duodenal ulcer have a poor outcome.

Patients and methods

Two hundred and sixty-one patients with duodenal ulcer proven by endoscopy were treated with cimetidine 1g/day (200 mg three times daily after meals and 400 mg at bedtime) till healing was complete as judged by endoscopy which was repeated every 4 to 6 weeks. They were then treated with cimetidine 400 mg at bedtime. Liquid or tablet antacids in small amounts were allowed for relief of mild symptoms. Endoscopy was done within a fortnight if there was a recurrence of pain or heartburn or acid regurgitation; but if asymptomatic a routine endoscopy was done approximately every 6 months. Those who had relapsed were retreated with cimetidine 1g/day till healed and the process repeated.

The value of maintenance treatment was assessed, albeit historically, by comparing the outcome with that of placebo maintenance in an investigation which immediately preceded the current study (Bardhan et al., 1982). In it, 180 of 248 patients whose duodenal ulcer had healed at one month on cimetidine 1g/day, were then maintained on placebo; most relapsed and on re-healing were entered into the current cimetidine maintenance programme.

Healing was defined as the complete disappearance of ulcer(s) and/or erosions and their replacement by intact mucosa which was normal or inflamed. Relapse or recurrence was the re-appearance of ulcer(s) or only erosions, or both. An ulcer was a lesion which had depth whereas erosions were small, yellow (the colour being similar to ulcers) but superficial. A relapse was classified as symptomatic when symptoms had occurred within one month before endoscopy, even if the patient was symptom free at the time of the examination; this was to take into account those with intermittent symptoms. A refractory duodenal ulcer was one that failed to heal on cimetidine 1g/day within 3 months (Bardhan, 1984).

The probability of relapse was calculated by standard life table analysis. The outcome of the first and

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second courses of treatment was compared using the generalized Wilcoxon test (Gehan, 1965). This study was part of a wider programme on the long-term treatment of duodenal ulcer and was approved by the Rotherham Health Authority Ethical Committee.

Results

Outcome of the first course of treatment

The probability of relapse increased with time but was highest during the first year of treatment. This was particularly so for symptomatic relapse, the cumulative probability was 20% at 1 year and only a further 5% (total 25%) at 2 years. Silent relapse was more common, the corresponding figures being 32% and 49%. No patient had haemorrhage or perforation at the time of relapse (Figure 1).

Outcome of the second course of maintenance treatment

A second course of maintenance treatment was given to 137 patients. The relapse rate during the second course was higher than during the first but was not significantly different. This is despite the bias, which may have occurred against patients on repeated treatment for having relapsed once they may have more aggressive disease. Again, no patient developed any ulcer complications at the time of relapse. Therefore, a second course of maintenance treatment is not necessarily more likely to fail than the first course (Figure 2).

Refractory versus non-refractory duodenal ulcer

Refractory duodenal ulcer (61 patients) was associated with a high and early probability of relapse; symptomatic 45% at 1 year and 48% at 2 years; silent 38% and 48% respectively. In contrast, relapse in those with non-refractory duodenal ulcer (200 patients) was likely to be both less frequent and slower: at 1 year and 2 years symptomatic 13% and 20%, silent 28% and 43% respectively (Figure 3).
Patients who without associated contrast, if rates were defined the calculating Table n total relapse was as lesion The absence of symptoms did not necessarily indicate an absence of disease; if there was a recurrence, the lesion was as likely to be an ulcer as erosions. In contrast, if there were symptoms, then there was a five times greater chance of the lesion being an ulcer (with or without associated erosions) than erosions alone (Table I).

The relation between lesions and symptoms

The likelihood to relapse with only erosions (i.e. no associated ulcer) steadily increased with time but the majority of patients were asymptomatic. After 2 years, of the 61 patients with refractory duodenal ulcer, 13 (21%) developed erosions alone but with symptoms in 3 patients (i.e. 5% of the 61). Amongst 200 patients with non-refractory duodenal ulcer, 36 (18%) developed erosions but only 7 patients (3% of the 200) were symptomatic.

Value of maintenance treatment

The definition of ulcer recurrence had an effect on calculating the relapse rate. When relapse was re-defined as the recurrence of an ulcer crater with or without associated erosions, i.e. excluding those patients who had erosions alone, the silent relapse rates were lower both in patients with refractory and with non-refractory ulcers, and this in turn reduced the total relapse rates (Table II).

The effect of the type of lesions on the calculation of relapse rates

Patients with erosions alone

The likelihood of relapse on placebo at 1 and at 2 years was respectively symptomatic 73% and 82%, silent 11% and 12%. In contrast on cimetidine 400 mg nightly relapse was less, markedly so for symptomatic recurrence ($P < 0.001$ for both total and symptomatic relapse). On cimetidine the chance of relapse at 1 and at 2 years was, respectively, reduced to: symptomatic 20% and 25%, silent 32% and 49% (Figure 4).

Table I  The relation between the type of lesion at relapse and symptoms based on 137 patients who relapsed

<table>
<thead>
<tr>
<th>Clinical state at time of relapse</th>
<th>Type of ulcer patient</th>
<th>Ulcer ± erosions</th>
<th>Erosions only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent</td>
<td>Non-refractory</td>
<td>28 (20%)</td>
<td>29 (21%)</td>
<td>39 (29%)</td>
</tr>
<tr>
<td></td>
<td>Refractory</td>
<td>16 (21%)</td>
<td>10 (7%)</td>
<td>26 (19%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Non-refractory</td>
<td>23 (17%)</td>
<td>7 (5%)</td>
<td>30 (22%)</td>
</tr>
<tr>
<td></td>
<td>Refractory</td>
<td>21 (15%)</td>
<td>3 (2%)</td>
<td>24 (17%)</td>
</tr>
</tbody>
</table>

Table II  The effect of the type of lesions on the calculation of relapse rates

<table>
<thead>
<tr>
<th>Cumulative relapse* at (months):</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>23%</td>
<td>75</td>
<td>40%</td>
</tr>
<tr>
<td>Silent</td>
<td>20</td>
<td>9%</td>
<td>34</td>
<td>18%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>34</td>
<td>14%</td>
<td>41</td>
<td>22%</td>
</tr>
<tr>
<td>Non-refractory ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>15%</td>
<td>35</td>
<td>29%</td>
</tr>
<tr>
<td>Silent</td>
<td>8</td>
<td>4%</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>19</td>
<td>11%</td>
<td>23</td>
<td>19%</td>
</tr>
<tr>
<td>Refractory ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>50%</td>
<td>40</td>
<td>73%</td>
</tr>
<tr>
<td>Silent</td>
<td>12</td>
<td>22%</td>
<td>22</td>
<td>40%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>15</td>
<td>28%</td>
<td>18</td>
<td>33%</td>
</tr>
</tbody>
</table>

*Relapse is now re-defined as the recurrence of ulcer(s) with or without erosions, i.e. excluding patients who had only erosions. By re-definition 88 patients were classed as having relapsed.
Adverse events

Adverse events were rare and no patient had to be withdrawn. One patient had breast tenderness which cleared spontaneously despite continued treatment; and another had arthralgia on healing doses (1g) of cimetidine with marked improvement when the dose was reduced to 400 mg at bedtime. These two patients were reported earlier (Bardhan et al., 1982). No clinically significant drug interactions were recognized.

Discussion

In this study we found that in patients with non-refractory duodenal ulcer, who form the vast majority of ulcer patients, the symptomatic relapse rate was low and that the chance of relapse diminished after the first year: 13% at 1 year and 20% at 2 years. On re-healing and on further maintenance treatment, the pattern is likely to repeat itself. This is despite the fact that as this group of patients have relapsed once already, a poorer outcome might have been expected. There are only few reports of maintenance treatment with cimetidine or ranitidine for longer than one year with which to compare our own, but other investigators, like ourselves, have observed that the relapse rate decreases markedly after the first year (Bianchi Porro et al., 1980; Bianchi Porro, 1982; Kratochvil & Brandstatter, 1983; Ström et al., 1984; Gray et al., 1982; Walan et al., 1985; Schutz, 1983; Boyd et al., 1984).

Three conclusions follow. First, those likely to develop a symptomatic relapse during maintenance treatment will commonly do so in the first year. Second, as a subsequent course of maintenance treatment is likely to be as effective as the first, a single relapse without complications is not necessarily an indication for abandoning such treatment. Third, there is reason to be cautiously optimistic that maintenance treatment will remain effective in the long-term and that it probably prevents relapse rather than merely postpone it.

Smoking (Sontag et al., 1984; McCarthy, 1984; Boyd et al., 1984), a long ulcer history (Gough et al., 1984) and pre-pyloric ulcers (Ström et al., 1984) have been reported to increase relapse rates during maintenance treatment. To these factors we add refractory duodenal ulcer, which in this centre was almost invariably associated with relapse.

Most studies of maintenance treatment with cimetidine are of one year’s duration (or less); we have therefore compared our relapse rates at one year with these results. The total (i.e. symptomatic plus silent) and symptomatic relapse rates we observed of 52% and 20% respectively are within the range found by others, but our silent relapse rate of 32% is higher. Thus, in 14 studies, the relapse at one year on average was: total 34% (range 13% to 65%); symptomatic 11% (range 8% to 32%); silent 8% (range 8% to 15%) (Misiewicz & Bradbury, 1984). Two patient groups contribute to our higher than average relapse rates: patients with refractory ulcer and patients who relapsed with erosions alone. When they are excluded, thereby making the remainder of the patients more comparable with those reported in other studies, the relapse rate fell: total 29%, symptomatic 19%, silent 10%. One possible explanation for the higher than usual incidence of duodenal erosions alone (i.e. without an ulcer) seen in our patients with non-refractory ulcer, is that they may have more severe disease than apparently similar patients reported in the literature. Thus our patients were put on maintenance treatment only after they had two or more relapses during placebo treatment (Bardhan et al., 1982) or during intermittent treatment (Bardhan, 1980). Patient selec-

![Figure 4](http://pmj.bmj.com/ on June 19, 2017 - Published by group.bmj.com)
tion and definition of recurrence can therefore substantially influence relapse rates.

For patient management, the most useful information on the outcome of maintenance treatment is the symptomatic relapse rate. Therefore, it is arguable whether silent relapse or recurrence of erosions alone should be included in calculating the relapse rate (which as a result is considerably increased); indeed most investigators do not. But we have used these indices partly to give a more complete picture of the outcome of treatment and partly because we view these events as markers of disease reactivation although clinically they may not be important.

None of our patients who relapsed, with or without symptoms, developed complications. We did not monitor the biochemistry of our patients but clinically none suffered any major adverse reaction on maintenance cimetidine treatment.

As a result of our findings, we no longer routinely use low dose maintenance treatment with cimetidine 400 mg at bedtime in patients with refractory duodenal ulcer; their medical management remains unsatisfactory and although several come to surgery the results of operation are, in our experience, often poor (Bardhan, 1984). In the non-refractory group of ulcer patients, such treatment does not necessarily suppress the disease; but it is an effective way of keeping the majority symptom-free both simply and with safety, and allows most patients to lead normal lives.

Acknowledgements

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References

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