Relapse Rate of Duodenal Ulcer After Cessation of Long-Term Cimetidine Treatment
A Double-Blind Controlled Study

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Patients with a healed duodenal ulcer and who were symptom-free following 12 months of maintenance treatment with cimetidine 400 mg twice daily were randomized double-blind to a further 6 months therapy with either cimetidine 400 mg twice daily or placebo 2 tablets twice daily. Twenty-six patients received placebo and 15 patients cimetidine. Relapse was defined as symptoms for 3 out of 7 consecutive days and ulcer recurrence was confirmed by independent endoscopy. One of 15 patients on cimetidine relapsed: 20 of 26 patients on placebo relapsed. This relapse rate (77%) is similar to that found in previous studies after only 6 weeks cimetidine therapy (71%). This study suggests that 12 months cimetidine does not change the tendency of duodenal ulcer to recur and that the relapse rate is no greater than after 6 weeks cimetidine.

The histamine H2 receptor antagonist cimetidine has now been in use in the therapy of duodenal ulcer disease for over 3 years. After healing a duodenal ulcer with a 4- to 6-week course of cimetidine, the frequency of relapse in European studies is 55-70% within 3 months and 75-90% within 12 months (1-4). In Australian studies, 45% of patients had relapsed within 3 months and 90% within 12 months (5, 6), and long-term maintenance therapy with cimetidine prevents this high recurrence rate (1-6).

The possibility that H2 receptor antagonists might enhance the tendency of ulcers to relapse has been raised by reports of complications soon after stopping short courses of the drug (7, 8). However, in double-blind trials, complications were uncommon in patients allocated to placebo maintenance therapy after short courses of cimetidine (1-6). The relapse rate after long-term maintenance cimetidine has been reported in open and uncontrolled studies (3).

The present controlled study was designed to establish the relapse rates after 1 year of continuous cimetidine therapy. Such a study would indicate whether prolonged therapy had beneficial or adverse effects on the natural history of duodenal ulcer disease and its complications.

MATERIALS AND METHODS

Studies were performed at Prince Henry's Hospital, Melbourne, and the Royal Adelaide Hospital, Adelaide, and were approved by the Research Advisory Committee of Prince Henry's Hospital and by the Research Review Committee of the Royal Adelaide Hospital. Advised con-
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sent was obtained from all patients. At both hospitals, a large number of patients with proven symptomatic duodenal ulcer have been managed on long-term maintenance cimetidine. All these patients had originally presented with chronic ulcer-type pain and were treated with cimetidine 200 mg tds and 400 mg nocte. After 6 weeks, all were asymptomatic and endoscopy demonstrated complete healing of their ulcer. They were then maintained on cimetidine 400 mg orally twice daily. Forty-one consecutive patients with proven duodenal ulcer who had remained symptom-free and were found to be endoscopically healed following 12 months of cimetidine 400 mg bd, formed the group studied.

Our initial aim was to cease active therapy and assess the relapse rate. However, it was decided to have a small group on active treatment to ensure that both patient and investigator were "blind." Thus, the patients were randomized double-blind into two unequal groups: 15 patients to active cimetidine 400 mg orally twice daily and 26 patients to identical placebo tablets.

Patients were seen as outpatients at monthly intervals for 6 months or immediately on relapse and symptoms assessed. Antacid tablets (Mylanta) were allowed for pain and indigestion. Patients were asked to refrain from taking salicylates, but no advice was given regarding smoking or alcohol consumption. Relapse was defined as a return of symptoms similar to those previously experienced for more than 3 days in seven. At relapse patients were endoscoped by two endoscopists, one not involved in the clinical follow-up. The ulcer was recorded as healed or unhealed. Endoscopic healing was defined as a duodenal cap free from crater or erosion. Duodenitis was not considered a relapse. Instruments used were Olympus GIF type K, and GIF type P2 (Olympus Corporation of America, New Hyde Park, New York). Endoscopy is planned at 12 months in all patients who remain asymptomatic to assess the recurrence rate of "silent" duodenal ulcer.

RESULTS

Table 1 shows that the cimetidine and placebo groups are comparable with respect to age, sex, duration of disease, and previous complications. The mean number of antacid tablets consumed per patient per month of treatment was 6 for the placebo and 1 for patients receiving cimetidine.

<p>| Age, Sex, Duration of Disease, and Previous Complications in Patients Treated with Cimetidine or Placebo |
|--------------------------------------------------|-----------|-----------------------|------------------|
| Age, Sex, Duration of Disease, and Previous Complications in Patients Treated with Cimetidine or Placebo | Age, Sex, Duration of Disease, and Previous Complications in Patients Treated with Cimetidine or Placebo |</p>
<table>
<thead>
<tr>
<th>Current study</th>
<th>Number entered</th>
<th>Total number relapsed at (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks at 1 g daily then 1 year at 400 mg bd</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Cimetidine 400 mg bd</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2 illustrates the cumulative number of patients in relapse after 1, 2, 3, and 6 months. Thus, only 1 of 15 patients relapsed in the cimetidine treated group while 20 of 26 patients have relapsed in the placebo group. So far, in all patients who have developed recurrence of ulcer-type symptoms, a duodenal ulcer has been confirmed at endoscopy. No false positive symptomatic relapses have been found in this study, that is, in all patients with recurrent symptoms, ulceration was diagnosed by the endoscopist who was unaware of the patient's clinical state.

Figure 1 compares the relapse rate after 12 months continuous cimetidine with that found from our previous studies following 6 weeks cimetidine (5, 6). The slopes of the curve are identical, thus suggesting that the relapse rates after either 6 weeks or 12 months cimetidine therapy are similar.

DISCUSSION

This study has shown that although 12 months of maintenance cimetidine therapy was able to keep patients symptom-free and without ulcer, it was followed by a high rate of recurrence on substituting placebo treatment. Indeed it is disappointing that the relapse rate after this prolonged therapy is precisely the same as that previously found after a 6-week course (5, 6, 9).

In the current study, all patients who developed ulcer symptoms during follow-up had a duodenal ulcer demonstrated at endoscopy. Periodic endoscopy in all patients was not performed, although routine endoscopy at 12 months is planned. Thus, detection of asymptomatic ulcer recurrence has not been studied. Our previous experience with long-term cimetidine (5, 6, 9) has shown that asymptomatic relapse occurs in placebo patients but has been very infrequent in the cimetidine-treated