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 affects 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-
sent was obtained from all patients. At both hospitals, a
large number of patients with proven symptomatic duode-
nal ulcer have been managed on long-term maintenance
cimetidine. All these patients had originally presented
with chronic ulcer-type pain and were treated with cimeti-
dine 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 ci-
methidine 400 mg orally twice daily. Forty-one con-
secutive patients with proven duodenal ulcer who had re-
mained symptom-free and were found to be endoscopi-
cally 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 ran-
domized double-blind into two unequal groups: 15 pa-
tients 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 tak-
ing salicylates, but no advice was given regarding smok-
ing or alcohol consumption. Relapse was defined as a re-
turn 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 con-
sidered a relapse. Instruments used were Olympus GIF
type K, and GIF type P2 (Olympus Corporation of Ameri-
cia, 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, du-
ration of disease, and previous complications. The
mean number of antacid tablets consumed per pa-
tient per month of treatment was 6 for the placebo
and 1 for patients receiving cimetidine.

<table>
<thead>
<tr>
<th>Table 1. Age, Sex, Duration of Disease, and Previous Complications in Patients Treated with Cimetidine or Placebo</th>
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<tbody>
<tr>
<td>Age, mean ± se (range)</td>
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<tr>
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<td>Cimetidine</td>
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<td>Placebo</td>
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*Previous perforation of hemorrhage.

Table 2 illustrates the cumulative number of pa-
tients 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 symp-
toms, a duodenal ulcer has been confirmed at en-
doscopy. 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 pa-
tient'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 fol-
lowed by a high rate of recurrence on substituting
placebo treatment. Indeed it is disappointing that
the relapse rate after this prolonged therapy is pre-
cisely 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 ul-
cer demonstrated at endoscopy. Periodic endosco-
py in all patients was not performed, although rou-
tine endoscopy at 12 months is planned. Thus, de-
tection of asymptomatic ulcer recurrence has not
been studied. Our previous experience with long-
term cimetidine (5, 6, 9) has shown that asympto-
matric relapse occurs in placebo patients but has
been very infrequent in the cimetidine-treated