Hospital Practice

FIVE-YEAR STUDY OF CIMETIDINE OR SURGERY FOR SEVERE DUODENAL ULCER DYSPEPSIA

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Summary   55 patients originally selected as candidates for elective ulcer surgery (one-third having had previous perforation or haemorrhage requiring transfusion) entered cimetidine trials over 5 years ago. 50 patients have been followed up over this period. 30 (60%) have not required ulcer surgery and the 12 who persisted with continuous therapy remain well. All the 18 who temporarily discontinued therapy had recurrence of symptoms, yet they remained well after re-establishing continuous maintenance therapy. Of the 20 patients who underwent ulcer surgery, 2 (10%) required further treatment for recurrent ulceration.

INTRODUCTION

THE efficacy of cimetidine in producing rapid symptom relief and in healing duodenal ulceration is well established.[1,2] There is also clear evidence that continuous low-dose maintenance cimetidine for up to 1 year prevents symptom and ulcer recurrence during the period of treatment.[3-7] However, recent work has shown that after withdrawal of such maintenance therapy the incidence and speed of relapse is very similar to that seen after shorter term courses of cimetidine.[5,8] Furthermore, the success or failure of maintenance therapy seems to be unaffected by the duration of acute-dose treatment.[9] Doubt therefore arises as to whether the natural history of duodenal ulcer has been significantly altered by maintenance therapy. Perhaps prolonged exposure to maintenance doses of the drug may confer lasting remission after cimetidine is finally withdrawn.

We report here the follow-up of a group of duodenal ulcer patients who have been on cimetidine for up to 5½ years. The report also examines how patients whose symptoms are not controlled by cimetidine maintenance therapy fare after surgery.

PATIENTS AND METHODS

55 of the patients who had been included initially in a 1-month acute trial of cimetidine (1 g/day)[2] followed by a 6-month double-blind controlled maintenance study[3] have continued to be followed up for another 60 months during which they were asked to take cimetidine 400 mg a night.

All patients had originally been accepted as candidates for elective ulcer surgery, but instead entered cimetidine studies.[2,3] A criterion for entry to the early studies was endoscopic (Olympus GIFK) evidence of duodenal ulceration despite treatment with various conventional antacid regimens. In no case was there evidence of any pyloric or duodenal narrowing at the time of entry to the study. One-third of the patients entering the initial trial had a history of either duodenal perforation or upper gastrointestinal haemorrhage requiring blood transfusion.[2,3]

During the original maintenance study 3 patients who had a relapse (mainly those allocated to placebo) were put back on "open"

cimetidine (1 g/day) for periods of up to 10 weeks to induce symptom relief and endoscopic healing, and then allocated to maintenance cimetidine (400 mg) orally at bedtime. If further relapse occurred in this extension to the maintenance study, symptom relief was sought either by recommencing 400 mg cimetidine at bedtime or by increasing the maintenance dose. In some cases intermittent full-dose therapy (1 g/day) was given until remission or until it was convenient to undergo elective surgery.

RESULTS

Complete follow-up information was available for 50 patients 5½ years after the start of the cimetidine studies. 5 patients were lost to follow-up after the first year. The 55 patients (44 men, 11 women) had a mean age of $45\cdot1\pm2\cdot3$(SD) years and an ulcer history for a mean of $12\cdot5\pm2\cdot2$ years; other details have been published previously.[2,3]

Surgery

After 60 months, 20 patients (40%) had undergone surgery—8 whose symptoms were poorly controlled by cimetidine and whose recurrence of symptoms and of ulceration (confirmed at endoscopy) occurred within 7 months of starting maintenance cimetidine; 7 who had ulcer complications (5, none of whom had evidence of pyloroduodenal narrowing at the time of entry to the cimetidine studies, for pyloric stenosis confirmed by barium meal and endoscopy, and 2 for continued bleeding); and 5 patients who requested ulcer surgery when attempts to manage without maintenance therapy proved unsuccessful. The standard surgical procedure was truncal vagotomy with drainage (gastrojejunostomy or pyloroplasty), but antrectomy and vagotomy was performed in the 2 patients who had continued bleeding, and in a third who responded to pentagastrin stimulation with a maximum acid output of 72 mmol/h.

14 of the 15 patients who required ulcer surgery because of ulcer symptoms or complications had their first relapse during the first year of maintenance therapy, and attempts to re-establish these patients on maintenance cimetidine 400 mg were attended by further relapse. In the 15th patient pyloric stenosis developed after he discontinued maintenance therapy during the third year of follow-up. Of the 5 patients who elected to have surgery, 3 were operated on in the 1st year and 2 in the 3rd year (see accompanying figure).
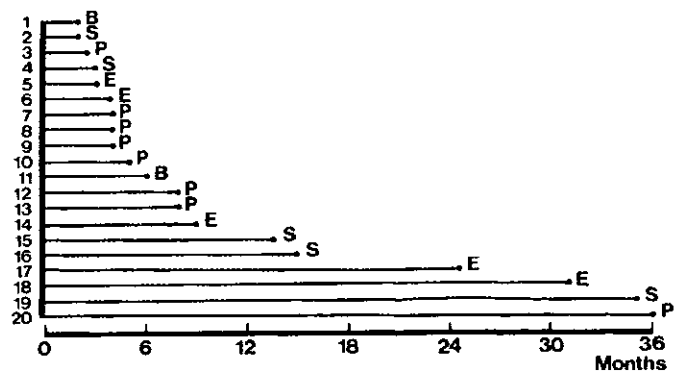
Timing and reasons for surgery in 20 duodenal ulcer patients.

P=recurrent pain; S=pyloric stenosis; E=elected to have surgery; B=bleed.

Recurrence after surgery.—Repeat endoscopy done 21–54 months postoperatively (median time 48 months) showed that the 18 who were symptomless since their operation had no ulcers on endoscopy, but that the 2 who had ulcer symptoms after surgery had recurrent ulceration. Acid-secretion studies indicated late positive Hollander responses to insulin testing and less than 50% reduction in maximum acid outputs to pentagastrin after vagotomy.

No Surgery

30 patients who, before the introduction of cimetidine, would have undergone elective ulcer surgery because of failed medical therapy, have avoided surgery for 60 months.

In our earlier double-blind controlled studies of maintenance dose therapy, treatment was judged to have failed when symptoms recurred and an ulcer was seen on endoscopy. In the present study failure is judged simply by return of ulcer-type symptoms because endoscopy was done only when surgery was imminent or after 3–4 years of follow-up.

All patients treated conservatively had been advised to continue with cimetidine 400 mg a night, but of the 30 who so far have avoided surgery only 12 did so. All 12 remained symptom-free, although of the 9 who underwent review endoscopy at 4 years 2 (who had been on maintenance therapy for at least 47 months) showed shallow duodenal ulceration. The other 3 patients had died from unrelated causes—namely, myocardial infarction at 10 months, ruptured aortic aneurysm at 24 months, and bronchial carcinoma at 35 months, but all were free from ulcer symptoms up to the time of their death.

Effect of Stopping Maintenance.

18 patients continued with maintenance therapy for varying periods but all at some stage stopped therapy because they felt well. Only 1 female patient, who had had 3 months' maintenance treatment, remained symptom-free for up to 4 years; the remaining 17 had recurrence of ulcer symptoms 7·0 (±0·9) weeks later. 9 of these were able to relieve their symptoms promptly by resuming nightly maintenance therapy, and only 1 had symptomless ulceration at the review endoscopy at 4 years. Higher dose therapy of 1 g/day was necessary for symptom relief in the other 8, who continue to require intermittent high-dose courses.

Side-effects

Only 1 patient, who later required surgery for bleeding ulcer, had side-effects which could be attributed to the drug. He complained of bilateral calf cramps, worse at night but eased by stopping therapy. He therefore treated himself with intermittent courses of cimetidine lasting 3 to 4 weeks followed by similar intervals off therapy. The fact that these calf cramps did not recur after surgery suggests they were related to cimetidine.

DISCUSSION

The results of this study show that in patients originally selected as candidates for surgery because of failure of conventional treatment to control a bad natural history, recurrence of ulcer symptoms invariably follows cessation of maintenance cimetidine therapy. In our original controlled trial[3] the mean time between withdrawal of treatment and

relapse was around 2 months; this extension to the study shows that the consequences of stopping or resuming cimetidine seem to be similar no matter when changes in therapy occurred over the 4-year follow-up. Indeed 8 of 17 patients who eventually relapsed when they discontinued maintenance cimetidine had been on the drug continuously for around 2 years or more. It would seem, therefore, that prolonging the duration of maintenance therapy does not increase the likelihood of a lasting remission after treatment is finally stopped.

One might speculate that those patients whose ulcer symptoms could not be controlled with maintenance cimetidine represent the difficult end of the peptic ulcer patient spectrum, and that they might fare equally badly after surgery. However, so far, of the patients who finally underwent truncal vagotomy and a drainage procedure, only 2 (12%) have had a recurrent ulcer. Poor response to cimetidine did not adversely affect the outcome of surgery. Nevertheless, it is of interest that after 5½ years of cimetidine a substantial proportion of patients (60%) originally selected as candidates for surgery have avoided surgical intervention, albeit at the expense of virtually continuous maintenance therapy. The eventual role of cimetidine in the management of severe duodenal ulcer dyspepsia may thus be determined by the patients' willingness to persist with regular maintenance therapy.

Surgery remains an obvious necessity for the recognised complications of duodenal ulcer. In this follow-up study 5 of 20 patients who underwent surgery did so for pyloric stenosis which developed during cimetidine maintenance therapy. These patients, who had had no endoscopic evidence of pyloroduodenal narrowing at entry to the cimetidine studies, had been symptom-free while on maintenance therapy until a short time before the detection of the classic clinical, radiological, and endoscopic findings and surgery. The question therefore that has to be answered is whether accelerated healing in response to cimetidine was a factor in such rapidly developing stenosis.

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TRICHOMONADS

The trichomonads have a fine flagellum
Which keep them young and agile
   (On the whole)
But can't escape our efforts to repel 'em
When we prescribe some Fl –
Metronidazole

H. E. M. KAY