PRACTICE OBSERVED

Practice Research

Long term management of duodenal ulcer in general practice: How best to use cimetidine?

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Abstract

Two hundred and sixty seven patients with duodenal ulceration were entered into a five year study of two strategies of treatment with cimetidine. Two thirds were treated continuously with 400 mg at bedtime supplemented by temporary increases in dosage if they had symptomatic relapses (group 1), and the remaining third were given intermittent "healing" doses for four to eight weeks if a symptomatic recurrence was judged to have occurred (group 2). Life table analysis showed that the probability of remaining free of clinically important symptoms five years after the start of treatment was 24% (95% confidence interval (CI) 15·5% to 32·6%) in group 1 compared with nil in group 2 ($p<0·0001$). The median values for the longest periods free from relapse for each patient were 108 weeks in group 1 and 32 weeks in group 2, respectively ($p<0·0001$; 95% CI of the median difference 36 to 76). Over the five years 10 patients suffered major complications, two requiring emergency surgery, while a further nine had elective surgery because of the failure of medical treatment. There were no deaths that could be attributed either to ulceration or to treatment with cimetidine.

Medical management was therefore very satisfactory for most patients, though those treated continuously with cimetidine suffered considerably less from their ulcer symptoms. As 80% of patients studied relapsed during the two years after a healing course of cimetidine, continuous treatment will benefit many patients treated in general practice.

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Introduction

When cimetidine was introduced in 1976 it was the first effective medical treatment for duodenal ulceration and was therefore likely to be taken by many people. Comprehensive monitoring of its safety was undertaken and the results of several investigations were published.[1-3] As part of the assessment of its safety some long term studies were set up, the present study being one of them. Though it was considered important to establish the safety of cimetidine, it was equally important to examine different schemes of medical management in view of the chronicity of peptic ulceration and the likelihood that most patients with duodenal ulcers would be treated in general practice.[4]

The Clydebank Health Centre was an ideal location for a long term study as it houses 11 general practices serving a relatively stable population of 65 000 patients. The study reported here is unique in that it is the only one that reports the results of treatment of a large group of patients with confirmed duodenal ulceration treated in a primary care setting.

Patients and methods

Between September 1979 and September 1981 patients attending the Clydebank Health Centre with symptoms suggestive of duodenal ulceration were referred to the study coordinator, who ran an evening clinic dedicated to the trial. Patients with either endoscopic or radiological evidence of duodenal ulceration within the previous two years and whose symptoms were similar to those with which they had originally presented were immediately entered into the study. All other patients were referred for upper gastrointestinal endoscopy, and only those with evidence of an active duodenal ulcer were subsequently included.

All patients in the trial thus had confirmed duodenal ulceration and were treated with the dose of cimetidine recommended at the time—namely, 200 mg three times daily with meals and 400 mg at bedtime. They were all treated for a minimum of eight weeks, as unpublished evidence at that time suggested that most ulcers could be expected to have healed after this period of treatment. Provision was made for patients to receive a further four to eight weeks' treatment with cimetidine 400 mg three times daily with meals and 400 mg at bedtime if their symptoms were not adequately controlled by the standard dose. Unmarked Rennie Digestif tablets were provided for each patient to take for further symptomatic relief whenever necessary.

Patients were seen after four, eight, 12, or 16 weeks. When they had achieved a satisfactory symptomatic response, defined as the time when their dyspeptic symptoms ceased to interfere with their work, sleep, or leisure activities, they were treated with cimetidine 400 mg daily at bedtime (group 1) or given no treatment (group 2). Randomisation in blocks of 12 according to a restricted randomisation method was carried out at the start of treatment with full doses of cimetidine. For every two patients assigned to the prospective regimen of continuous treatment one received no treatment. Thereafter patients were seen every three months unless they suffered a relapse determined on clinical grounds only. This was defined as appreciable pain occurring on three consecutive days or two consecutive nights. A more important event—for example, a perforation or gastrointestinal bleeding sufficient to require operation or blood transfusion—resulted in withdrawal from the study. A symptomatic relapse was treated with cimetidine 1 g or 1·6 g daily, depending on the dose which had originally been required to produce an adequate clinical response. Patients were then treated according to their original randomisation unless they had more than two relapses within a year, in which case patients in group 2 were transferred to group 1 and patients in group 1 were either given cimetidine in full doses or referred to a surgeon. The study was not "blinded" because we wished to reflect the ordinary circumstances of general practice as closely as possible.

Patients could see the study coordinator whenever they liked, so relapses could be treated without delay. They also kept diary cards to aid memory. Details of patients were entered on to a standard form at each visit to the clinic and the progress of each patient was tracked on a master chart so that every attempt could be made to trace non-attenders. There was a crude check on compliance, and patients were encouraged to take their medication regularly, but they were not excluded from the study if they did not do so.

For the statistical analysis only data recorded before a change of treatment group were considered. Life table analysis was used to calculate the probability of remaining free from relapse at the end of each month of the study. The probabilities for both treatment groups were calculated using the Kaplan-Meier estimate.[5] The Gehan-Wilcoxon test was used to compare the longest times free from relapse for both groups.[6] Both these tests take account of censored observations—that is, the time for which a patient was known to be free of relapse and then lost to follow up. The χ^2 test was used to compare the differences between treatment groups in the number of days of pain experienced by the patients.

Results

Two hundred and sixty seven patients entered the study during the two year recruitment period and this report covers the period up to September 1985.

Of the original 267 patients 23 defaulted during the first eight weeks of healing treatment and of the remaining 244 a further 23 patients (9%) were excluded before statistical analysis as their initial treatment phase with full doses of cimetidine lasted longer than 16 weeks. These patients may have had so called "refractory" ulcers though they did not have further endoscopic assessments. It is, however, noteworthy that 11 of these patients remained in the study for the five year period, they all ultimately needed continuous treatment, and they suffered between none and nine relapses each. Thus about half the 23 patients were eventually relieved of their symptoms and their initial failure to respond to cimetidine cannot easily be explained. They probably had more severe peptic ulceration and hence may have constituted a different subgroup of patients. Two more patients were wrongly assigned to their treatment group and were also excluded. Thus the results in 219 patients were analysed, 152 of whom were randomised to group 1 and 67 to group 2.

The demographic characteristics of these patients are shown in table I; there were no significant differences between the groups. The median (range) ages were 43 (17-75) in group 1 and 46 (19-68) in group 2. About two thirds of the patients were smokers or ex-smokers, about a fifth drank more than five pints of beer a week, and about one tenth drank more than five measures of spirits a week.

TABLE I—*Demographic characteristics of the two groups*

	Patients receiving continuous treatment (group 1, n=152) No (%)	Patients receiving intermittent treatment (group 2, n=67) No (%)
Men	108 (71)	43 (64)
Women	44 (29)	24 (36)
Eating habits:		
Regular	99 (65)	47 (70)
Not regular	18 (12)	6 (9)
Unknown	35 (23)	14 (21)
Consumption of beer (pints/week):		
0-5	118 (78)	55 (82)
5 or more	34 (22)	12 (18)
Consumption of spirits (measures/week):		
0-5	138 (88)	60 (90)
5 or more	14 (12)	7 (10)
Smoking habits:		
Smokers	83 (55)	39 (58)
Non-smokers	22 (14)	14 (21)
Ex-smokers	20 (13)	4 (6)
Unknown	27 (18)	10 (15)

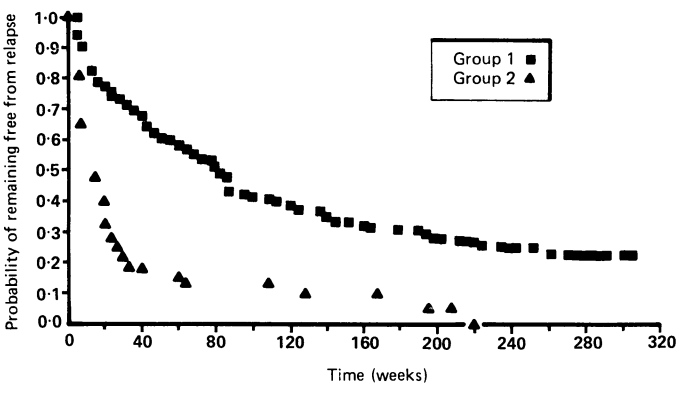
EFFICACY

Patients remaining free from relapse

The probability of remaining free from relapse at the end of each month is shown in figure 1, and after five years was 24% for group 1 (95% confidence interval (CI) 15·5% to 32·6%) compared with nil for group 2 ($p<0·0001$). In practice, however, after five years 12 patients (8%) in group 1 were known not to have suffered a relapse compared with none in group 2, although a further 44 patients (29%) in group 1 had failed to attend for their three monthly review but were known to have remained free from relapse until their last attendance (table II). Thus over five years as many as 56 patients (37%) given a healing course of cimetidine followed by continuous lower dose treatment may not have suffered a symptomatic relapse compared with as many as six (9%) of the group treated with intermittent doses. During the

TABLE II—*Outcome in patients during the study. Figures are given as number (percentage) in each group*

	Year				
	1	2	3	4	5
Group 1 (n=152)					
Patients who had had a relapse:					
Those who defaulted	6 (4)	20 (13)	27 (18)	52 (34)	81 (53)
Those who remained in study	51 (34)	60 (39)	62 (41)	42 (28)	15 (10)
Patients who had not had a relapse:					
Those who defaulted	16 (10)	22 (14)	28 (18)	32 (21)	44 (29)
Those who remained in study	79 (52)	50 (33)	35 (23)	26 (17)	12 (8)
Group 2 (n=67)					
Patients who had had a relapse:					
Those who defaulted	18 (27)	45 (67)	49 (73)	55 (82)	59 (88)
Those who remained in study	36 (54)	11 (16)	9 (13)	5 (7)	2 (3)
Patients who had not had a relapse:					
Those who defaulted	3 (4)	3 (4)	4 (6)	5 (7)	6 (9)
Those who remained in study	10 (15)	8 (12)	5 (7)	2 (3)	0



Life table analysis of probability of remaining free from relapse.

first year of treatment the probability of staying free from relapse according to the stringent criteria imposed was 60% for patients in group 1 and 17% for patients in group 2 (fig 1) (95% CI 52·3% to 68·4% and 7·6% to 26·3%, respectively). The estimated difference in these probabilities was 43% (95% CI 31·0% to 55·7%).

Patients suffering a relapse

Pain—Because of the problem of decreasing numbers of patients particularly in group 2 the proportion of days when pain was experienced by each patient was analysed only during the first year. The study was not designed specifically to compare the amount of pain in the two groups, as the onset of pain was considered to be a marker of symptomatic relapse. Because patients were given immediate access to medical care, any difference in the incidence of pain between the groups was likely to be minimised. Patients in group 1 nevertheless had significantly less pain than patients in group 2 ($p<0·05$) (table III).

TABLE III—*Incidence of pain during first year of study*

	No (%) of patients with no pain	No (%) of patients with pain for <10% of days	No (%) of patients with pain for 10% of days or more
Group 1	45 (30)	84 (55)	23 (15)
Group 2	10 (15)	38 (57)	19 (28)

Rate of relapse—Table IV shows the rates of relapse for each group. The trend was always in favour of group 1 with the difference at the end of the first year being particularly striking. During the first year 18 patients in group 2 were transferred to group 1 because of two relapses and 17 patients were transferred in the second year for the same reason. Altogether 42 (63%) patients in group 2 needed continuous treatment because of frequent relapse—that is, two or more a year.

TABLE IV—*Rate of relapse in each year of study*

	Group 1		Group 2	
Year	No of patient months at risk	Relapse rate/ 100 patient months	No of patient months at risk	Relapse rate/ 100 patient months
1	1593	4·71	563	17·23
2	1323	5·37	293	6·83
3	1162	4·39	176	5·68
4	969	4·95	110	7·27
5	519	2·89	52	3·85

Periods free from relapse—The longest periods free from relapse for each patient were compared between the two groups. The median values were 108 and 32 weeks for groups 1 and 2 respectively ($p<0·0001$), median difference 56 weeks, 95% CI of the median difference 36 to 76.

Complications—We reviewed the records of 242 of the original 267 patients, the remaining 25 having moved away from the Clydebank district. Nine patients suffered episodes of gastrointestinal bleeding. One of these, who was taking cimetidine at the time, did not have a frank bleed but his haemoglobin concentration fell from 109 to 67 g/l over nine months. He also had multiple sclerosis and was taking prednisolone 10 mg daily, which could have contributed to the blood loss. Four of the remaining eight patients were receiving cimetidine at the time that they bled. Eleven patients underwent surgery, two requiring emergency operations. One had vagotomy and pyloroplasty carried out after a haematemesis, while the other had a perforation closed and was receiving cimetidine at the time of the perforation. The remaining nine patients underwent elective operations either because cimetidine failed to control their symptoms or because they did not wish to continue medical treatment.

SAFETY

Nine patients died, four from ischaemic heart disease, one from acute myeloblastic leukaemia, one from a carcinoma of the bronchus, one from motor neurone disease, one from diabetic ketoacidosis, and one from drowning. None of the deaths were considered to be related to treatment with cimetidine. In addition four patients were withdrawn while taking cimetidine because of adverse events, though none seemed to be related to treatment. One woman was withdrawn after four years because of symptoms and signs of fluid retention. Three men were withdrawn, one who had a right hemicolectomy for Crohn's disease; one (who was taking no other treatment) who had dryness of the mouth, eyes, and nose together with failure of ejaculation; and one who had constipation requiring admission to hospital after four years in the study.

Discussion

Boyd and Wormsley have implied that all patients with duodenal ulcers should receive continuous medical treatment, as the ulcers should not be allowed to relapse because of the associated dangers.[7] Other authors have argued that treatment should be reserved for patients who suffer symptomatic relapse, and that only a minority require continuous treatment.[8] Our study, unique in general practice, compared these two philosophies. Relapse was diagnosed only symptomatically, even if symptoms occurred for only a relatively short time. This, however, mirrors the usual sequence of events in general practice.

A completely successful medical treatment for duodenal ulceration would be one that did no harm but, at the same time, kept the patient free of symptoms and prevented complications. How do our results measure up to this ideal? The data suggest that there was no major risk inherently due to cimetidine. None of the deaths that occurred in the study were directly due to taking cimetidine, nor were any of the adverse events that resulted in stopping of the treatment. Continuous treatment with cimetidine was twice as effective as intermittent treatment in keeping patients free of pain during the first year of the study, with just under one third reporting no pain at all. It was not practical to compare the two methods of treatment for longer than a year as the numbers of patients receiving intermittent treatment declined rapidly because those with more aggressive disease were transferred to group 1. In addition the ease with which patients with symptoms were able to obtain medical help would tend to minimise any difference between continuous and intermittent treatment.

The probability of remaining free of important dyspeptic symptoms for five years while taking cimetidine continuously was 24% compared with nil after four years on intermittent treatment. After one year the probability of being free from relapse while taking cimetidine continuously was 60%, and this compares with 82% of 1726 patients symptomatically assessed in a study undertaken in hospital.[9] It should be remembered, however, that no patient was excluded from our study because of failure to comply with the treatment regimen, and patients in group 1 not taking their medication who suffered a recurrence were therefore assumed to be on continuous treatment for the purpose of the analysis. Conversely, only 17% of the patients in our study could be expected not to have a recurrence of symptoms within a year of receiving a healing course of cimetidine, which contrasts with the 36% reported by Bardhan.[8] This difference may reflect the strict definition of relapse which we imposed.

The continuous use of cimetidine was considerably more effective in preventing recurrence of symptoms compared with intermittent courses. Although most patients who were free of pain were also likely to be free of ulceration,[10] cimetidine did not prevent complications. Nine patients had clinically important episodes of bleeding and one had a perforation; thus the incidence of complications in the study was about 0·5% per year. This compares favourably with the incidence of 3-5% reported in a study undertaken in hospital in which patients were followed up for about the same period, though much of that survey had been carried out before the introduction of cimetidine.[11]

Overall, however, our data illustrate Pounder's assertion that the decisive effect of cimetidine on duodenal ulceration is produced not by short courses during acute attacks but by maintenance treatment.[12] It is tempting, therefore, to suggest that all patients with duodenal ulceration should receive continuous treatment with an H_2 antagonist. This would mean, however, that a proportion of

patients would receive unnecessary medication. Although the life table analysis suggested that the probability of remaining free from relapse after a healing course of cimetidine was nil over a five year period, it could have been 9% if those who were asymptomatic at the time they were lost to follow up had remained so. Thus perhaps one in 10 patients with confirmed duodenal ulceration requires a course of cimetidine to heal the ulcer and no further treatment. These patients may then stay free from recurrence for up to five years. The other 90% of patients can, however, expect further clinically important symptoms. At best only about a fifth of these could expect to stay free of symptoms for two years, the likelihood being that most would relapse within a year (table V). How many symptomatic recurrences should therefore be allowed to occur before continuous treatment is started? Cimetidine has been shown to be a safe drug in the 11 years since its introduction. In the light of this experience we therefore conclude that a reasonable policy in general practice would be to treat any patient having two or more relapses within two years with continuous maintenance treatment. We cannot predict at this stage how long this should be continued, though we hope in due course to be able to report whether five years' treatment with cimetidine influences the course of the disease.

TABLE V—*Number (percentage) of patients according to their longest time free of relapse*

	Longest time free of relapse (years)					
	0-1	1-2	2-3	3-4	4-5	>5
Group 1	35 (23)	40 (26)	32 (21)	19 (13)	14 (9)	12 (8)
Group 2	43 (64)	11 (16)	6 (9)	6 (9)	1 (2)	0 (0)

We thank all those who contributed to the study, particularly Mr Ross McCallum, who carried out the initial endoscopies, the doctors who referred patients, Mrs Cath Myers, who organised the ulcer clinic, Mrs M W Spencer-Mills and Mrs J Cornhill, who managed the data, Mr David Carter of Smith Kline and French, who did the statistical analysis, and, not least, the patients.

References

1 Burland WL. Evidence for the safety of cimetidine. In: Cruetzfeldt W, ed. *Proceedings of an international symposium on histamine H_2 receptor antagonists*. Amsterdam: Excerpta Medica, 1978:238-55.
2 Davis TG, Pickett DL, Schlosser JH. Evaluation of a worldwide spontaneous reporting system with cimetidine. *JAMA* 1980;**243**:1912-4.
3 Colin-Jones DG, Langman MJS, Lawson DH, Vessey MP. Post-marketing surveillance of the safety of cimetidine: twelve-month morbidity report. *Q J Med* 1985;**54**:253-68.
4 Fry J. Peptic ulcer: a profile. *Br Med J* 1964;ii:809-12.
5 Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *Journal of the American Statistical Society* 1958;**53**:457-81.
6 Gehan EA. A generalised Wilcoxon test for comparing arbitrarily single censored samples. *Biometrika* 1965;**52**:203-23.
7 Boyd EJS, Wormsley KG. Natural history of duodenal ulcer. *Survey of Digestive Diseases* 1985;**3**:230-9.
8 Bardhan KD. Intermittent treatment of duodenal ulcer with cimetidine. *Br Med J* 1980;**281**:20-2.
9 Bianchi-Porro G. Tagamet: new dimensions. *Report of the proceedings of a symposium held at the international congress of gastroenterology, Lisbon, Portugal*. Windermere Communications, 1984: 33-8.
10 Burland WL, Hawkins BW, Beresford J. Cimetidine treatment for the prevention of recurrence of duodenal ulcer: an international collaborative study. *Postgrad Med J* 1980;**56**:173-6.
11 Elashoff JD, Van Deventer G, Reedy TJ, *et al*. Long term follow up of duodenal ulcer patients. *J Clin Gastroenterol* 1983;**5**:509-15.
12 Pounder RE. Model of medical treatment for duodenal ulcer. *Lancet* 1981;i:29-30.

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ONE HUNDRED YEARS AGO

As the weeks wear on, the opposition to the scheme promoted by the London Colleges of Surgeons and Physicians for obtaining for themselves exclusive powers for granting medical degrees to their members and licentiates in the future, widens and gathers strength. The University of Oxford has thrown its weight into the balance against the two Colleges, and the University of Cambridge is preparing to take the same course. Moreover, the London medical schools, although largely controlled by councillors of the two Colleges, and therefore slow to move in the matter, are beginning to awaken to the imperfections and dangers of a scheme which, while promising them much, offers the gift in so doubtful a shape that not even a supposed self-interest can blind them to the serious defects by which the scheme is disfigured. We have already pointed these out, and some of them are clearly indicated in the memorial from the Westminster Hospital Medical School. That memorial, which is drawn up with a full recognition of the advantages to London medical schools of reasonable facilities for acquiring the degree of medicine in London for the students whom they train, points out the palpable fact that of all the schemes which are now before the Privy Council, that of the two Colleges is the least satisfactory.

It is unsatisfactory for three main reasons—first, because it fails to give to the body entrusted with this new degree-giving power even a reasonably representative constitution. Neither the teachers as such, nor the competent colleges and medical schools as such, nor the graduates are represented in it. The degree-giving power would be given to a Senate, in which the teaching bodies of London would have no representative voice. The colleges and medical schools would have no power of appointing delegates to express their united opinions on any subject of teaching or examination, nor would the persons who sit on the Senate be in any way responsible to the schools for their votes or acts, or on any occasion be called upon to give an account to them of their proceedings. Again, the graduates of the university, to whom its interests, its reputation, and its development will be at least as dear and as important as to any other persons, would, by the proposed constitution, be totally excluded from any right to representation on the governing body of their own university. This is an anomaly of which we know no other example. The whole constitution of the university is imposed upon it by the self-elected and non-representative Council of the College of Physicians, and by the most inadequately constituted and imperfectly representative Council of the College of Surgeons. No security is taken that the University would be administered otherwise than in the corporate interests of those two licensing bodies, and, in fact, every precaution is taken to prevent any interest which can be supposed to conflict with the individual and joint interests of those two bodies from being allowed even to have a voice in the management of the new University.

The spirit in which it is likely to be administered is further indicated by the fact that it is not proposed to constitute this new body as a degree-giving power for the students of medical schools of London, all educated alike, under the same conditions, with the same curriculum, and with the same clinical and scientific advantages. But it is proposed to take from them the right of choice as to the portals through which they will present themselves for this higher grade, and to confine their selection exclusively to these two particular licensing bodies. In the name and with the object of granting degrees to the London medical students, an effort is made by this proposal for a charter practically to tie them up to selection of the Membership of the College of Surgeons and the licence of the College of Physicians as the sole mode of entrance. Thus, whether it be regarded from the point of view of the relation of the teaching bodies to the examining bodies, or from the point of view of a just and fair constitution of the University, or from the point of view of fairness to the medical students themselves, the proposition stands condemned. Most persons will agree with the memorial of the Westminster School in the opinion that of all the schemes before the Privy Council that of the College of Physicians is the most objectionable.

With the immense body of opposition which has now arisen to that scheme, in the profession at large, as represented by the Society of General Practitioners and the Apothecaries' Society, by the Scotch Universities, by the English Universities, and by the feeling in the medical schools which the Westminster memorial expresses, it is hardly conceivable that the Privy Council can adopt any other course than that which we have from the first advocated, of appointing a Royal Commission fully to inquire into the whole subject, and to arrange a scheme which shall meet all the just requirements of the case.

(*British Medical Journal* 1888;i:364)