PAPERS AND ORIGINALS

Cimetidine: an advance in gastric ulcer treatment?

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Summary and conclusions

Sixty patients with endoscopically confirmed gastric ulceration took part in a single-blind trial of cimetidine 1 g daily compared with conventional treatment—namely, carbenoxolone in patients aged under 60 and Caved-(S) in those over 60.

Twenty-nine patients received cimetidine: in 12 (41%) ulcer healing was complete after one month, in 26 (90%) healing was complete after two months, and all ulcers were healed after three months of treatment. In the under-60s, ulcers were healed in a greater proportion of patients given cimetidine than in those given carbenoxolone. The difference, however, was significant only at the 5% level, which owing to small numbers was of doubtful clinical validity. In the over-60s cimetidine and Caved-(S) were of similar efficacy.

The 54 patients with healed ulcers are being followed up for two years; so far there have been 16 recurrences (30%). Further trials are needed, which should include maintenance treatment aimed at lowering the unacceptable high recurrence rate.

Introduction

Clinical trials of the histamine H₂-receptor antagonist cimetidine have shown that it may be an effective and safe treatment for gastric ulceration.¹⁻⁷ Two questions, however, need to be answered: Should cimetidine be accepted as the treatment of

choice in gastric ulceration? and Is maintenance treatment needed once ulcer healing has been achieved? We have conducted a trial comparing cimetidine with conventional medical treatment—namely, carbenoxolone for patients aged under 60 and Caved-(S) for the over-60s. Treatment was continued for up to three months or until healing occurred if sooner. The patients were completely unselected, and in some 40% of cases the ulcer was first diagnosed after hospital admission for gastrointestinal bleeding. Once ulcer healing was achieved treatment was stopped and the patient carefully followed up for evidence of recurrence.

Patients and methods

The study was performed concurrently at two hospitals using identical protocols and in accordance with the Declaration of Helsinki. The nature of the trial was fully explained to the patients before entry and their informed consent obtained.

Drug treatment and dosage—All patients with proved gastric ulceration who were suitable for medical care were allocated at random to one of four treatment groups according to a code held and administered solely by the pharmacy. Thus we did not know which treatment the patients were receiving. Those under 60 were given either cimetidine, 200 mg three times a day and 400 mg at night, or carbenoxolone, at an initial dose of 100 mg thrice daily for one week but then reduced to 50 mg thrice daily. Patients over 60 received either cimetidine (1 g daily) or Caved-(S), two tablets three times a day between meals. All patients were given antacids (Rennies) to take as required. They received no specific dietary advice but were discouraged from smoking. A personal diary card was completed daily recording severity of symptoms, number of antacids taken, and drug compliance. Treatment was given for up to three months but stopped when healing occurred.

Initial investigations and follow-up—Endoscopy was performed in all cases before patients entered the trial to exclude malignancy. The size and site of ulcers were usually assessed radiologically; ulcers were defined as small (cross-sectional area less than 50 mm²), medium (50-200 mm²), and large (over 200 mm²). The patients were followed up monthly with either a barium meal or endoscopy. Ulcer healing was always checked by endoscopy and defined as complete epithelial regeneration at the ulcer base. Treatment was considered to have failed when an ulcer remained unhealed after three months or the patient was withdrawn from the trial because of complications or failure to control symptoms. At each outpatient attendance the patients were asked about symptoms and possible adverse reactions to treatment. Haematological and biochemical screening, performed

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every two or four weeks, comprised full blood count; erythrocyte sedimentation rate; blood urea, electrolyte, and serum creatinine concentrations; and liver function tests.

Follow-up after healing—All patients were reviewed at three-monthly intervals, radiography or endoscopy or both being used in those with further symptoms. Most patients underwent routine radiography after six months of follow-up to exclude asymptomatic recurrence. A pentagastrin test meal was performed on three-quarters of patients with recurrences.

Statistical—The results were analysed with Fisher's exact test or Bernoulli's binomial distribution test.

Results

Between January 1976 and February 1978, 67 patients entered the trial. Seven were subsequently withdrawn. Two were found on biopsy to have unsuspected gastric cancer; three underwent surgery, two for continuing gastrointestinal bleeding and one for an incarcerated hiatus hernia with obstruction; one died from a cerebrovascular accident; and one was withdrawn owing to a generalised rash during treatment with cimetidine. The remaining 60 patients form the basis of this report.

TREATMENT GROUPS

The four treatment groups were evenly matched for age (table I). There was some variation in sex ratio, but this was not significant. Most of the under-60s were smokers, whereas only half of the over-60s smoked ($P < 0.001$).

Twenty-eight patients had their gastric ulcer diagnosed after emergency admission to hospital, 25 because of acute gastrointestinal

TABLE I—Details of treatment groups studied

Treatment group	No of patients	Age (years)		Sex		Smoking habit	
		Mean	Range	M	F	Smokers	Non-smokers
Patients aged under 60							
Carbenoxolone ..	12	49	25-58	4	8	10	2
Cimetidine ..	9	48	25-58	7	2	9	
Patients aged over 60							
Cimetidine ..	20	68	61-77	11	9	10	10
Caved-(S) ..	19	70	61-84	8	11	10	9

TABLE II—Details of patients diagnosed after emergency admission to hospital

Treatment group	Total No of patients	No of inpatients	No of trial days spent in hospital		Reason for admission
			Mean	Range	
Patients aged under 60					
Carbenoxolone	12	4	11	3-23	Gastrointestinal bleeding (3); abdominal pain (1)
Cimetidine ..	9	4	7	2-13	Gastrointestinal bleeding
Patients aged over 60					
Cimetidine ..	20	8	9	3-30	Gastrointestinal bleeding (7); chest pain (1)
Caved-(S) ..	19	12	8	1-16	Gastrointestinal bleeding (11); abdominal pain (1)

TABLE III—Initial size of ulcers in the four treatment groups

Treatment group	No of patients	Initial ulcer size			
		Small	Medium	Large	
<i>Patients aged under 60</i>					
Carbenoxolone	12	5	4	3	
Cimetidine	9	2	4	3	
<i>Patients aged over 60</i>					
Cimetidine	20	5	11	4	
Caved-(S)	19	3	13	3	

bleeding and three because of initially undiagnosed abdominal or chest pain (table II). The ratio of inpatients to outpatients was similar in all four treatment groups, as was the average number of trial days spent in hospital. There was no appreciable difference between the groups in the distribution of initial ulcer size (table III).

ULCER HEALING

After two and seven weeks of treatment two patients in the carbenoxolone group were withdrawn because of uncontrolled dyspepsia. A further three had ulcers that remained unhealed after three months (table IV). In the under-60s cimetidine group all nine patients had

TABLE IV—Effect of treatment on ulcer healing

Treatment group	No of patients	Cumulative No of patients with ulcers healed at:			Significance (Fisher's exact test)
		1 month	2 months	3 months	
Patients aged under 60					
Carbenoxolone ..	12	4	7	7	} P = 0.039
Cimetidine ..	9	3	9	9	
Patients aged over 60					
Cimetidine ..	20	9	17	20	} NS
Caved-(S) ..	19	9	15	18	

healed ulcers after two months. In the over-60s cimetidine group 17 of the 20 patients had healed ulcers at two months, and all ulcers were healed after three months. In the Caved-(S) group 15 of the 19 patients achieved ulcer healing at two months and 18 by the end of treatment. One patient was withdrawn after five weeks because of a recurrence of symptoms, which was further complicated by a gastrointestinal bleed.

In the under-60s there was a difference in healing rates in favour of cimetidine. This was significant at the 5% level. There was no such difference, however, between cimetidine and Caved-(S) (table IV). Similarly, no significant correlation could be found between the rate of ulcer healing and initial ulcer size, ulcer site, initial inpatient or outpatient treatment, or smoking habit.

RELIEF OF SYMPTOMS

Analysis of the diary cards showed only minor differences between the four groups in the relief of symptoms.

Under-60s—Patients in both treatment groups entered the trial with similar degrees of dyspepsia (day and night pain) and showed no appreciable difference in their rather slow response to treatment.

Over-60s—The pretreatment severity of daytime dyspepsia was similar in the two treatment groups. There was a trend in favour of Caved-(S) from the third week, which just reached significance by the fourth week ($P < 0.05$). Patients in the Caved-(S) group had less night pain before treatment ($P < 0.05$), and their response to treatment was similar to that in the cimetidine group until the third week, when once again a response in favour of Caved-(S) just reached significance ($P < 0.05$).

SIDE EFFECTS

One patient developed a generalised rash while taking cimetidine and another became severely hypertensive while taking carbenoxolone. Except for these cases no major clinical, haematological, or biochemical problems were encountered.

RESULTS OF FOLLOW-UP

We plan to follow up for two years the 54 patients in whom ulcer healing was achieved.

Ulcer recurrence

There have been 16 recurrences (table V), 14 of which occurred within nine months of healing. This recurrence rate (30%) may well

TABLE V—Results of follow-up (numbers of recurrences given in parentheses)

Treatment group	No of patients followed up	No of recurrences	Duration of follow-up (months)					
			-3	-6	-9	-12	-18	-24
Patients aged under 60								
Carbenoxolone	7	3	7 (1)	6	4 (1)	2	2 (1)	
Cimetidine ..	9	2	9	7 (2)	4	4	4	3
Patients aged over 60								
Cimetidine ..	20	6	20 (2)	18 (4)	12	10	6	3
Caved-(S) ..	18	5	18 (1)	15 (1)	13 (2)	9	7 (1)	2

underestimate the final figure. No asymptomatic recurrences were found on routine radiography.

Factors affecting recurrence

Initial inpatient treatment was the only factor found to affect ulcer recurrence; there were only three recurrences among the 25 inpatients compared with 13 among the 29 patients treated wholly as outpatients (Fisher's exact test: $P < 0.05$).

Factors not affecting recurrence

Speed of ulcer healing—Twenty-five ulcers healed with one month of treatment, and nine recurred. Twenty-three ulcers healed with two months of treatment, and five recurred. Six ulcers took three months to heal, and two recurred.

Initial ulcer size—Of the 12 small ulcers, six recurred; of the 29 medium-sized ulcers, nine recurred; and of the 13 large ulcers one recurred.

Ulcer site—Sixteen patients had ulcers in the antrum, and there were five recurrences; 24 had mid-body ulcers, and seven recurred; and 14 had upper-body ulcers, and four recurred.

Treatment group—Ulcers recurred in all treatment groups (table V)—in three out of seven patients given carbenoxolone, eight out of 29 given cimetidine, and five out of 18 given Caved-(S).

Sex—There were nine ulcer recurrences among the 27 men, and seven among the 27 women.

Age—Recurrence occurred in five of the 16 patients aged under 60, and 11 of the 38 aged over 60.

Smoking—Of the 33 smokers, 10 had recurrences; and of the 21 non-smokers, six had recurrences.

Previous history—Of the 16 patients with ulcer recurrences, nine had a previous history of peptic ulceration. Such a history was present in only 12 of the 38 who had not had a recurrence.

Acid secretion studies—Pentagastrin studies on 11 out of the 16 patients with ulcer recurrence showed a nearly normal scatter (mean basal acid output 6.3 mmol (mEq)/h (range 0.1–27.3), total acid output 17.9 mmol/h (0.5–30.2), and maximum acid output 32.4 mmol/h (1.0–39.6)).

Discussion

Cimetidine was first used for gastric ulceration by Pounder *et al* in 1976.¹ In an uncontrolled pilot study they recorded rapid relief of symptoms and complete healing in 10 patients after six weeks of treatment. Six endoscopically controlled trials^{2–8} then yielded healing rates of 69–79% after four or six weeks of treatment. This contrasted with rates of 48% with carbenoxolone,² 41–61% with high-dose antacids,^{6,7} and 28–50% with placebo.^{3–5} We compared cimetidine with conventional medical treatment. Carbenoxolone was chosen for patients under 60, but because of its potential side effects—namely, hypokalaemia, fluid retention, and hypertension^{8,9}—older patients were given Caved-(S).

Previous studies of cimetidine have aimed to assess its healing effect on gastric ulceration. Treatment periods have usually been short (four to six weeks) and healing rates have been between 69% and 79%. What is not known is whether a 100% healing rate would have been achieved if treatment had been continued for three months. We have tried to answer this by assessing

ulcer healing at monthly intervals and defining failure as non-healing after three months of continuous treatment. Endoscopy was performed at the start of the study to exclude cancer, as in a Veterans Administration co-operative study¹⁰ one in 25 patients thought to have a benign ulcer turned out to have an underlying carcinoma. We used radiography for follow-up, since this permitted an easier assessment of ulcer size. Healing, however, was always checked by endoscopy, and the end-point of the study was complete epithelial regeneration at the ulcer base.

In our study cimetidine was accompanied by gastric ulcer healing. Among the 29 patients treated a healing rate of 41% (12 cases) was achieved at one month, rising to 90% (26) at two months and 100% at three months. One patient developed a drug eruption necessitating his withdrawal from the trial. Otherwise side effects were minimal, and results of laboratory safety tests were all essentially normal.

In the patients under 60 cimetidine was slightly more successful in producing ulcer healing than carbenoxolone ($P = 0.039$). Owing to the small number of patients in this subgroup (21) the clinical validity of this is uncertain. Nevertheless, cimetidine appears to have fewer serious side effects than carbenoxolone, and so may ultimately replace it for the treatment of gastric ulceration.

In patients over 60 there was no appreciable difference in gastric ulcer healing rates between the Caved-(S)-treated and cimetidine-treated groups. Caved-(S) used in the dosage employed in this study, however, is only a quarter of the price of cimetidine, and may have fewer side effects. We cannot comment on the use of Caved-(S) in patients under 60 but would expect similar results.

During follow-up some 30% of the healed gastric ulcers recurred within 18 months irrespective of the treatment regimen. In the Veterans Administration co-operative study 42% of ulcers that had originally healed recurred within two years.¹⁰ Similarly Piper *et al* in a four-year study¹¹ found a recurrence rate of 26% in patients discharged from hospital with healed ulcers compared with 61% in patients discharged before ulcer healing. In our study the only factor that appeared to influence the recurrence rate was a period of initial inpatient treatment, which, although it did not speed ulcer healing, apparently reduced the incidence of recurrence (from 45% to 12%).

From this and other studies it seems that medical treatment will heal most gastric ulcers. The problem that remains is to prevent their recurrence.^{12,13} Some two-thirds of our patients were over 60 and were not ideal for gastric surgery. An effective maintenance treatment is therefore needed, and two studies have suggested cimetidine.^{14,15}

Preliminary results of our two-year follow-up study suggest that all future studies on gastric ulcer treatment should include maintenance therapy.

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Addendum

Since this paper was written there have been five more ulcer recurrences, bringing the total to 21. The ulcer recurrence rate is therefore now 39%.

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Genetic basis of rheumatoid disease: HLA antigens, disease manifestations, and toxic reactions to drugs

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Summary and conclusions

Ninety-five patients with rheumatoid arthritis and 200 healthy controls were examined for HLA-D-related (HLA-DR) alloantigens. HLA-DRW4 was significantly more prevalent among the patients and was particularly common in those with a family history of the disease (77% of such patients had DRW4 compared with 34% of controls). Significantly fewer patients than controls had DRW2: patients with this antigen had rheumatoid nodules less frequently and significantly lower titres of rheumatoid factor than patients without DRW2. In contrast DRW3 was significantly more prevalent among severely affected patients with rheumatoid factor titres exceeding 1/1280 and in patients with nodules. There was a significant association between DRW2 and DRW3 and toxic reactions to sodium aurothiomalate and penicillamine.

The results suggest that the HLA-DR phenotype is associated not only with susceptibility to rheumatoid arthritis but also with severity of the disease and whether certain toxic reactions to drugs occur.

Introduction

Studies on patients with rheumatoid arthritis (RA) have shown no consistent substantial association between the disease and any HLA-A-locus or B-locus antigens¹⁻³ but a highly significant association between RA and DRW4.^{6,7} Attempts to detect HLA-D-locus products serologically have led to the discovery of an allelic series of antigens that are detectable on B lymphocytes but not on most recirculating T lymphocytes. These antigens correlate significantly with the HLA-D antigens and are determined either by the D locus or by a very closely linked locus.⁸ Owing to uncertainty whether the B-lymphocyte alloantigens are determined by the HLA-D locus itself these

alloantigens have been provisionally designated HLA-D-related (HLA-DR).⁹ One B-lymphocyte alloantigen was detected by us in 74.4% of patients with RA but in only 27% of normal controls,¹⁰ and studies carried out as part of the seventh Histocompatibility Workshop and independently^{11,12} have shown that the B-lymphocyte alloantigen DRW4 is significantly associated with RA.

RA is associated with extra-articular manifestations such as nodules, cutaneous vasculitis, peripheral neuropathy, Sjögren's syndrome, and fibrosing alveolitis. During treatment with drugs, especially gold compounds and penicillamine, toxic reactions may occur. These include rashes, proteinuria, and reduced numbers of circulating leucocytes and platelets. Some of these toxic reactions and the extra-articular manifestations may be mediated immunologically.¹³⁻¹⁸

We decided to re-examine the association between erosive RA and the DR antigens and investigate the possible relation between HLA antigens and extra-articular manifestations of the disease and toxic reactions to sodium aurothiomalate and penicillamine.

Subjects and methods

Ninety-five Caucasian patients with classical or definite rheumatoid arthritis according to the ARA criteria¹⁹ were studied. Except for these ethnic and clinical criteria no selection was made. The group comprised 63 women and 32 men aged 29-76 years. We looked for extra-articular manifestations both at the time of the study and retrospectively in the case notes. This disclosed 39 patients with rheumatoid nodules, five with vasculitis, nine with rheumatoid lung, and two with peripheral neuropathy. A few patients had other clinical complications, nine having Sjögren's syndrome and one Felty's syndrome.

A total of 59 patients had been given courses of either sodium aurothiomalate (50 mg monthly) or penicillamine (up to 1200 mg daily) or both. Thirty had received only sodium aurothiomalate, 23 sodium aurothiomalate and penicillamine, and six only penicillamine. Toxic reactions were monitored by periodic urine analyses, blood counts, and physical examination. Since toxic reactions are particularly common during the first six months of treatment, patients had to be free of symptoms of toxicity for at least this period of treatment to be scored as drug-reaction negative.

Direct questioning was used to elicit a family history of RA and the age at onset of the disease.

IMMUNOLOGICAL TESTS

The highest recorded differential agglutination titre for rheumatoid factor as detected by the sensitised sheep red blood cell technique of Rose-Waaler was noted. This test was performed in several routine laboratories on widely separated occasions, however, so we decided to

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