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Maintenance therapy: a two year comparison between Caved-S and cimetidine treatment in the prevention of symptomatic gastric ulcer recurrence

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SUMMARY Eighty two patients with an endoscopically healed gastric ulcer, were treated for two years with either Caved-S tablets, two twice daily or cimetidine 400mg at night. During the first year, 12% (four out of 34) of the Caved-S group and 10% (four out of 41) of the cimetidine group had an ulcer recurrence. By the end of the second year, the recurrence rate was 29% (nine out of 31) in the Caved-S group, and 25% (eight out of 32) for the cimetidine group. Ulcer relapse occurred frequently in patients with either a dyspeptic history of over six months ($p<0.05$), or a past history of a gastric ulcer ($p<0.001$). Ulcers recurred rapidly after maintenance therapy; Caved-S two out of 22; cimetidine seven out of 23, within four months (NS). This study shows that long term maintenance therapy is safe and reasonably effective. The high recurrence rate after stopping treatment suggests that therapy in high risk or elderly patients should be for life.

In 1982 we published the results of a comparison between cimetidine and Caved-S in the treatment of gastric ulceration, with the preliminary results of the subsequent two year period of maintenance therapy.[1] In this paper we present the final results of that study, and also review the place of such treatment in the prevention of gastric ulcer recurrence.

Methods

PATIENTS

Eighty two patients with healed gastric ulcers were treated for two years with either Caved-S (deglycyrrhizinated liquorice, antacids, and up to 1980 bismuth subcitrate) two tablets twice daily or cimetidine 400mg at night. They were seen as outpatients at three monthly intervals. All patients with a return of symptoms lasting for more than a few days were endoscoped. After six months treatment, a barium meal was carried out. Standard haematological and biochemical screening was undertaken at six monthly intervals. All patients who completed the study were then followed up for a further four months.

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STATISTICAL METHODS

The Log-rank test as described by Peto *et al*[2] was used to compare ulcer recurrence in the two groups, and to look for factors influencing it.

Results

The two treatment groups were evenly matched for all important parameters (Table 1). The recurrence rate in the two groups was similar (NS see Table 2). During the two years treatment, approximately a quarter of the patients relapsed.

The withdrawal rate for the two year treatment periods were similar (Table 3). One patient with an antral ulcer healed on Caved-S, developed a gastric cancer high on the lesser curve 16 months later. The safety screening programme picked up one patient on cimetidine who developed abnormal liver function tests (SGPT 109) but these returned to normal within two months of stopping treatment.

Within four months of stopping maintenance therapy, nine ulcers recurred, seven in patients who had been on cimetidine, and two in those on Caved-S (NS see Table 2).

The duration of ulcer disease, and a past history of gastric ulcer predispose to ulcer recurrence ($p<0.05$ and $p<0.001$ respectively). Recurrence is not influenced by initial treatment, sex, age, smok-

Table 1 *Comparability of treatment groups*

		Population distribution before 2 year maintenance	
		Caved-S (40)	*Cimetidine (42)*
Sex	Male	14	19
	Female	26	23
Age	20–59	14	21
	≥60	26	21
Duration of ulcer disease	<6 months	16	15
	6 months–5 years	11	13
	>5 years	13	14
Previous proven ulcer	DU	4	3
	GU	10	10
	unknown/peptic	1	1
Smoking	Yes	21	28
Alcohol	Nil/minimal	28	31
	<10–>20 pints/week	12	11
Recent anti-inflammatories	Yes	5	10
Ulcer healing	6 weeks	29	30
	12 weeks	11	12
Ulcer size	<1 cm	12	6
	1–2 cms	17	27
	>2 cms	11	9
Ulcer site	Antral	7	6
	Incisural	5	2
	Body	20	25
	High lesser curve	8	9

ing, or drinking habits, ulcer size or site, inpatient treatment at the start of therapy or non-steroidal anti-inflammatory drug therapy.

Discussion

Modern treatment methods will heal the majority of gastric ulcers in two to three months, but ulcer recurrence is known to be rapid once therapy is stopped (30–90% within a year).[3–10] Unlike duodenal ulcers, gastric ulcers occur mainly in the elderly. About 20% may be related to non-steroidal anti-inflammatory drug therapy, and many patients have multiple pathology. Almost a quarter present with either haematemasis or melaena, and in the elderly this carries a high mortality. It is because of such risk factors that a safe and effective maintenance therapy has so much to offer.

Our two treatment regimes were equally effective. During the first year 12% of the Caved-S group, and 10% of the cimetidine group had an ulcer recurrence. After two years treatment this

Table 2 *Results of two years maintenance treatment and subsequent four month follow up*

	Caved-S	*Cimetidine*
Year one		
Started Year 1	40	42
Withdrawn	6	1
Ulcer recurrences	4 (12%)	4 (10%)
Year two		
Started year 2	30	37
Withdrawn	3	9
Ulcer recurrences	5 (19%)	4 (14%)
Combined results for year 1 and 2		
Withdrawn	9	10
Ulcer recurrences	9 (29%)	8 (25%)
Four month follow up after treatment		
Started	22	24
Withdrawn	0	1 (died)
Ulcer recurrences	2 (9%)	7 (30%)

Table 3 *Reasons for withdrawal*

	Treatment group	
	Caved-S	*Cimetidine*
Year one	2 died	1 died
	1 severe oesophagitis	
	2 too frail to attend	
	1 lost to follow up	
Year two	1 surgery for gastric cancer	3 died
		1 surgery for leiomyoma
	1 too frail to attend	1 raised SGPT (109)
	1 lost to follow up	2 lost to follow up
		1 stopped treatment
		1 recurrence of symptoms (not endoscoped)

had risen to 29% and 25% respectively. In a previous study we followed a similar group of unselected patients, not on maintenance therapy, for two years and found a recurrence rate of 33% after one year, rising to 44% at the end of two years.

A review of the literature[3–10] shows a one year recurrence rate on maintenance therapy of 0–21% but few studies have continued beyond this (Table 4).

The incidence of asymptomatic ulcer recurrence is unclear. Hentschel and coworkers[6] found that 24% of the relapses in their study were asymptomatic. In a recent review of maintenance therapy with ranitidine,[11] only 7% of the ulcer recurrences were asymptomatic. We looked for asymptomatic ulcer recurrence by radiology after six months treatment and found two ulcers. The importance of an ulcer recurrence that produces neither symptoms nor complications is unknown.

This study confirms that two years of maintenance therapy with either Caved-S or cimetidine will reduce symptomatic ulcer recurrence safely and effectively. Patients with a past history of gastric ulceration and dyspeptic symptoms of more than six months duration are more likely to have a recurrence during therapy ($p<0.05$ and $p<0.001$ respectively). These patients may require full healing dosage for maintenance therapy to keep them in remission.

How long should maintenance therapy be continued? In an attempt to answer this question, the patients were followed for a further four months after maintenance therapy was stopped. Twenty per cent of these patients developed an ulcer recurrence within this observation period, two out of 22 (9%) in the Caved-S group and seven out of 23 (30%) in the cimetidine group (NS). This rapid gastric ulcer recurrence after stopping maintenance therapy has not been recorded previously although it is well recognised in duodenal ulcer disease.[12 13]

During the four month period, one of the patients (who had previously been on cimetidine), presented with a severe gastrointestinal bleed from a large recurrent ulcer, and died after surgery. Maintenance therapy should perhaps be for life in the elderly or those with multiple pathology, particularly as the standard operation for gastric ulcer is a Bilroth I partial gastrectomy, with its associated mortality and morbidity.

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References

1 Morgan AG, McAdam WAF, Pacsoo C, Darnborough A. Comparison between cimetidine and Caved-S in the treatment of gastric ulceration, and subsequent maintenance therapy. *Gut* 1982; **23:** 545–51.

2 Peto R. *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II. *Br J Cancer* 1977; **35:** 1–39.

3 La Brooy SJ, Taylor RH, Ayrton C, *et al.* Cimetidine

Table 4 *Review of maintenance studies in gastric ulcer disease*

Author	Drug and dosage	Patients (no)	% Recurrence Follow up (m) 6–7	11–12	24	Drug and Dosage	Patients (no)	% Recurrence Follow up (m) 6–7	11–12	24	
	Cimetidine					*Placebo*					
La Brooy, Taylor, Ayrton, *et al*[3]	200 mg qid	15	13	—	—		14	21	—	—	NS
Machell, Ciclitira, Farthing, *et al*[4]	200 mg tds 400 nocte	11	—	18	—		14	—	86	—	<0.002
Birger Jensen, Møllmann, Rahbek, *et al*[5]	400 mg bd	10	—	0	—		9	—	55	—	<0.025
Hentschel, Schütze, Weiss, *et al*[7]	400 mg nocte	42	—	14	—		42	—	55	—	<0.001
Barr, Kang, Canalese, *et al*[7]	400 mg bd	24	—	21	—		25	—	48	—	0·02<p<0·05
			—	—	33		—	—	—	52	NS
	Ranitidine										
Cockel, Dawson, Jain[8]	150 mg nocte	19	6	—	—		20	42	—	—	<0·05
Hellier, Gent, Walker, *et al*[9]	150/100 mg nocte	32	6	—	—		12	33	—	—	<0·05
Alstead, Ryan, Holdsworth[10]	150 mg nocte	15	—	7	—		16	—	69	—	<0·005

in the treatment of gastric ulceration (GU). Abstract E26.5 Cimetidine 2774 *Hepatogastroenterology* 1980; suppl: 205.
4 Machell RJ, Ciclitira PJ, Farthing MJG, Dick AP, Hunter JO. Cimetidine in the prevention of gastric ulcer relapse. *Postgrad Med J* 1979; **55:** 393–5.
5 Birger Jensen K, Møllmann KM, Rahbek I, Rask Madsen J, Rune SJ, Wulff HR. Prophylactic effect of cimetidine in gastric ulcer patients. *Scand J Gastroenterol* 1979; **14:** 175–6.
6 Hentschel E, Schütze, Weiss W, *et al.* Effect of cimetidine treatment in the prevention of gastric ulcer relapse: a one year double blind multicentre study. *Gut* 1983; **24:** 853–6.
7 Barr GD, Kang JY, Canalese J, Piper DW. A two-year prospective controlled study of maintenance cimetidine and gastric ulcer. *Gastroenterology* 1983; **85:** 100–4
8 Cockel R, Dawson J, Jain S. Ranitidine in the long-term treatment of gastric ulcers. In: Misiewicz JJ, Wormsley KG, eds. *The clinical use of ranitidine* Oxford: Medicine Publishing Foundation, 1982: 232–8.
9 Hellier MD, Gent AE, Walker J, Britten D, Hutchison C, Gough KR. Ranitidine in the treatment of gastric ulcers: healing and maintenance. *Scand J Gastroenterol* 1982; **17** suppl 78: 615.
10 Alstead EM, Ryan FP, Holdsworth CD, Ashton, Moore M. Ranitidine in the prevention of gastric and duodenal ulcer relapse. *Gut* 1983; **24:** 418–20.
11 Record CO. Maintenance treatment with ranitidine in peptic ulceration. In: Tytgat GN, ed. *Ranitidine, the selective new H2-receptor antagonist.* Proceedings of Glaxo International Symposium, Amsterdam, 17–18 September 1982. Guildford: Theracom, 1982: 20–4.
12 Dronfield MW, Batchelor AJ, Larkworthy W, Langman MJS. Controlled trial of maintenance cimetidine treatment in healed duodenal ulcer: short and long-term effects. *Gut* 1979; **20:** 526–30.
13 Baron JH, Alexander-Williams J, Bennett JR. Cimetidine and duodenal ulcer. *Br Med J* 1979; **1:** 169–73.