Low dose maintenance treatment with cimetidine in duodenal ulcer: intermediate-term results

K.D. Bardhan, R.F.C. Hinchliffe and K. Bose

District General Hospital, Moorgate Road, Rotherham S60 2UD, UK.

Summary: Ulcer relapse rates during up to 2 years of prophylactic low-dose maintenance therapy (LDMT) with cimetidine 400 mg at bedtime was examined in 261 patients. Endoscopy was repeated every 6 months if asymptomatic, or whenever symptoms recurred. Relapse was defined as the recurrence of an ulcer crater or erosions or both.

In patients with non-refractory duodenal ulcer (those healed within 3 months) who comprise the majority, their likelihood of relapse at 6, 12, 18 and 24 months was: symptomatic 8%, 13%, 18%, 20%; silent 14%, 28%, 38%, 43%, respectively. In contrast, in patients with refractory ulcer, their symptomatic relapse rates were 36%, 45%, 46%, 48%, and silent 28%, 38%, 46%, 48% respectively. The outcome of a second course of LDMT was similar to the first. Narrowing the definition of relapse to exclude recurrence of erosions alone but without an ulcer decreased asymptomatic relapse in non-refractory ulcer patients by about half. No patient had any major side effects.

Thus, LDMT is a safe and effective way of keeping most patients with duodenal ulcer symptom free over 2 years.

Introduction

Low dose maintenance treatment (LDMT) with cimetidine at the standard dose of 400 mg at bedtime following healing of duodenal ulcer, markedly reduces the relapse rate over the next year (Burland *et al.*, 1980; Misiewicz & Bradbury, 1984), but little is known of the outcome of longer periods of treatment. We therefore present our results of up to 2 years' follow-up. We have investigated the symptomatic and silent relapse rates and have observed that patients with a refractory duodenal ulcer have a poor outcome.

Patients and methods

Two hundred and sixty-one patients with duodenal ulcer proven by endoscopy were treated with cimetidine 1g/day (200 mg three times daily after meals and 400 mg at bedtime) till healing was complete as judged by endoscopy which was repeated every 4 to 6 weeks. They were then treated with cimetidine 400 mg at bedtime. Liquid or tablet antacids in small amounts were allowed for relief of mild symptoms. Endoscopy was done within a fortnight if there was a recurrence of pain or heartburn or acid regurgitation; but if asymptomatic a routine endoscopy was done approximately

every 6 months. Those who had relapsed were re-treated with cimetidine 1g/day till healed and the process repeated.

The value of maintenance treatment was assessed, albeit historically, by comparing the outcome with that of placebo maintenance in an investigation which immediately preceded the current study (Bardhan *et al.*, 1982). In it, 180 of 248 patients whose duodenal ulcer had healed at one month on cimetidine 1g/day, were then maintained on placebo; most relapsed and on re-healing were entered into the current cimetidine maintenance programme.

Healing was defined as the complete disappearance of ulcer(s) and/or erosions and their replacement by intact mucosa which was normal or inflamed. Relapse or recurrence was the re-appearance of ulcer(s) or only erosions, or both. An ulcer was a lesion which had depth whereas erosions were small, yellow (the colour being similar to ulcers) but superficial. A relapse was classified as symptomatic when symptoms had occurred within one month before endoscopy, even if the patient was symptom free at the time of the examination; this was to take into account those with intermittent symptoms. A refractory duodenal ulcer was one that failed to heal on cimetidine 1g/day within 3 months (Bardhan, 1984).

The probability of relapse was calculated by standard life table analysis. The outcome of the first and

Correspondence: K.D. Bardhan, D.Phil. (Oxon), F.R.C.P.
Accepted: 11 December 1985

second courses of treatment was compared using the generalized Wilcoxon test (Gehan, 1965). This study was part of a wider programme on the long-term treatment of duodenal ulcer and was approved by the Rotherham Health Authority Ethical Committee.

Results

Outcome of the first course of treatment

The probability of relapse increased with time but was highest during the first year of treatment. This was particularly so for symptomatic relapse, the cumulative probability was 20% at 1 year and only a further 5% (total 25%) at 2 years. Silent relapse was more common, the corresponding figures being 32% and 49%. No patient had haemorrhage or perforation at the time of relapse (Figure 1).

Outcome of the second course of maintenance treatment

A second course of maintenance treatment was given to 137 patients. The relapse rate during the second course was higher than during the first but was not significantly different. This is despite the bias, which may have occurred against patients on repeated treatment for having relapsed once they may have more aggressive disease. Again, no patient developed any ulcer complications at the time of relapse. Therefore, a second course of maintenance treatment is not necessarily more likely to fail than the first course (Figure 2).

Figure 1 The probability of relapse in the 261 patients with healed duodenal ulcer during the first course of low dose maintenance treatment with cimetidine 400 mg at bedtime: symptomatic, silent and symptomatic plus silent (total) relapse rates: ● total, △ silent, ▲ symptomatic.

Figure 2 The probability of relapse during the second course of low dose maintenance treatment with cimetidine 400 mg at bedtime: symptomatic, silent and total relapse: ● total, △ silent, ▲ symptomatic.

Refractory versus non-refractory duodenal ulcer

Refractory duodenal ulcer (61 patients) was associated with a high and early probability of relapse; symptomatic 45% at 1 year and 48% at 2 years; silent 38% and 48% respectively. In contrast, relapse in those with non-refractory duodenal ulcer (200 patients) was likely to be both less frequent and slower: at 1 year and 2 years symptomatic 13% and 20%, silent 28% and 43% respectively (Figure 3).

Figure 3 The probability of relapse during the first course of low dose maintenance treatment with cimetidine 400 mg at bedtime: refractory ($n = 61$) versus non-refractory ($n = 200$) duodenal ulcer. Symptomatic and total (symptomatic plus silent) relapse rates: ▲ refractory total; ● non-refractory total; △ refractory symptomatic; ○ non-refractory symptomatic.

Table I The relation between the type of lesion at relapse and symptoms based on 137 patients who relapsed

<i>Clinical state at time of relapse</i>	<i>Type of ulcer patient</i>	<i>Ulcer ± erosions</i>	<i>Erosions only</i>	<i>Total</i>
Silent	Non-refractory	28 (20%)	29 (21%)	83 (61%)
	Refractory	16 (21%)	10 (7%)	
Symptomatic	Non-refractory	23 (17%)	7 (5%)	54 (39%)
	Refractory	21 (15%)	3 (2%)	

The relation between lesions and symptoms

The absence of symptoms did not necessarily indicate an absence of disease; if there was a recurrence, the lesion was as likely to be an ulcer as erosions. In contrast, if there were symptoms, then there was a five times greater chance of the lesion being an ulcer (with or without associated erosions) than erosions alone (Table I).

The effect of the type of lesions on the calculation of relapse rates

The definition of ulcer recurrence had an effect on calculating the relapse rate. When relapse was re-defined as the recurrence of an ulcer crater with or without associated erosions, i.e. excluding those patients who had erosions alone, the silent relapse rates were lower both in patients with refractory and with non-refractory ulcers, and this in turn reduced the total relapse rates (Table II).

Patients with erosions alone

The likelihood to relapse with only erosions (i.e. no associated ulcer) steadily increased with time but the majority of patients were asymptomatic. After 2 years, of the 61 patients with refractory duodenal ulcer, 13 (21%) developed erosions alone but with symptoms in 3 patients (i.e. 5% of the 61). Amongst 200 patients with non-refractory duodenal ulcer, 36 (18%) developed erosions but only 7 patients (3% of the 200) were symptomatic.

Value of maintenance treatment

The likelihood of relapse on placebo at 1 and at 2 years was respectively symptomatic 73% and 82%, silent 11% and 12%. In contrast on cimetidine 400 mg nightly relapse was less, markedly so for symptomatic recurrence ($P < 0.001$ for both total and symptomatic relapse). On cimetidine the chance of relapse at 1 and at 2 years was, respectively, reduced to: symptomatic 20% and 25%, silent 32% and 49% (Figure 4).

Table II The effect of the type of lesions on the calculation of relapse rates

	<i>Cumulative relapse* at (months):</i>							
	<i>6</i>		<i>12</i>		<i>18</i>		<i>24</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
All patients								
Total	54	23%	75	40%	85	54%	88	64%
Silent	20	9%	34	18%	43	28%	44	32%
Symptomatic	34	14%	41	22%	42	26%	44	32%
Non-refractory ulcer								
Total	27	15%	35	29%	38	42%	39	50%
Silent	8	4%	12	10%	15	16%	16	20%
Symptomatic	19	11%	23	19%	23	26%	23	30%
Refractory ulcer								
Total	27	50%	40	73%	47	85%	49	95%
Silent	12	22%	22	40%	28	51%	28	55%
Symptomatic	15	28%	18	33%	19	34%	21	40%

*Relapse is now re-defined as the recurrence of ulcer(s) with or without erosions, i.e. excluding patients who had only erosions. By re-definition 88 patients were classed as having relapsed.

Figure 4 The probability of relapse during maintenance treatment on placebo (O), $n = 180$, compared with low dose maintenance treatment on cimetidine (●), $n = 261$. The left-hand figure shows silent plus symptomatic (total) and the right, symptomatic only.

Adverse events

Adverse events were rare and no patient had to be withdrawn. One patient had breast tenderness which cleared spontaneously despite continued treatment; and another had arthralgia on healing doses (1g) of cimetidine with marked improvement when the dose was reduced to 400 mg at bedtime. These two patients were reported earlier (Bardhan *et al.*, 1982). No clinically significant drug interactions were recognized.

Discussion

In this study we found that in patients with non-refractory duodenal ulcer, who form the vast majority of ulcer patients, the symptomatic relapse rate was low and that the chance of relapse diminished after the first year: 13% at 1 year and 20% at 2 years. On re-healing and on further maintenance treatment, the pattern is likely to repeat itself. This is despite the fact that as this group of patients have relapsed once already, a poorer outcome might have been expected. There are only few reports of maintenance treatment with cimetidine or ranitidine for longer than one year with which to compare our own, but other investigators, like ourselves, have observed that the relapse rate decreases markedly after the first year (Bianchi Porro *et al.*, 1980; Bianchi Porro, 1982; Kratochvil & Brandstatter, 1983; Ström *et al.*, 1984; Gray *et al.*, 1982; Walan *et al.*, 1985; Schutz, 1983; Boyd *et al.*, 1984).

Three conclusions follow. First, those likely to develop a symptomatic relapse during maintenance treatment will commonly do so in the first year. Second, as a subsequent course of maintenance treatment is likely to be as effective as the first, a single relapse without complications is not necessarily an indication for abandoning such treatment. Third,

there is reason to be cautiously optimistic that maintenance treatment will remain effective in the long-term and that it probably prevents relapse rather than merely postpone it.

Smoking (Sontag *et al.*, 1984; McCarthy, 1984; Boyd *et al.*, 1984), a long ulcer history (Gough *et al.*, 1984) and pre-pyloric ulcers (Ström *et al.*, 1984) have been reported to increase relapse rates during maintenance treatment. To these factors we add refractory duodenal ulcer, which in this centre was almost invariably associated with relapse.

Most studies of maintenance treatment with cimetidine are of one year's duration (or less); we have therefore compared our relapse rates at one year with these results. The total (i.e. symptomatic plus silent) and symptomatic relapse rates we observed of 52% and 20% respectively are within the range found by others, but our silent relapse rate of 32% is higher. Thus, in 14 studies, the relapse at one year on average was: total 34% (range 13% to 65%); symptomatic 11% (range 8% to 32%); silent 8% (range 8% to 15%) (Misiewicz & Bradbury, 1984). Two patient groups contribute to our higher than average relapse rates: patients with refractory ulcer and patients who relapsed with erosions alone. When they are excluded, thereby making the remainder of the patients more comparable with those reported in other studies, the relapse rate fell: total 29%, symptomatic 19%, silent 10%. One possible explanation for the higher than usual incidence of duodenal erosions alone (i.e. without an ulcer) seen in our patients with non-refractory ulcer, is that they may have more severe disease than apparently similar patients reported in the literature. Thus our patients were put on maintenance treatment only after they had two or more relapses during placebo treatment (Bardhan *et al.*, 1982) or during intermittent treatment (Bardhan, 1980). Patient selec-

tion and definition of recurrence can therefore substantially influence relapse rates.

For patient management, the most useful information on the outcome of maintenance treatment is the symptomatic relapse rate. Therefore, it is arguable whether silent relapse or recurrence of erosions alone should be included in calculating the relapse rate (which as a result is considerably increased); indeed most investigators do not. But we have used these indices partly to give a more complete picture of the outcome of treatment and partly because we view these events as markers of disease reactivation although clinically they may not be important.

None of our patients who relapsed, with or without symptoms, developed complications. We did not monitor the biochemistry of our patients but clinically none suffered any major adverse reaction on maintenance cimetidine treatment.

As a result of our findings, we no longer routinely use low dose maintenance treatment with cimetidine 400 mg at bedtime in patients with refractory duodenal ulcer; their medical management remains unsatisfactory and although several come to surgery

the results of operation are, in our experience, often poor (Bardhan, 1984). In the non-refractory group of ulcer patients, such treatment does not necessarily suppress the disease; but it is an effective way of keeping the majority symptom-free both simply and with safety, and allows most patients to lead normal lives.

Acknowledgements

The Day Ward and the endoscopy nursing and clerical staff coped with increasing pressure; Dr C.D. Holdsworth provided valuable comments; the Medical Illustrations Departments at the Royal Hallamshire Hospital, Sheffield and at this hospital, provided the figures; Beverley Mason typed the manuscripts; the Rotherham Health Authority continues to support such studies. We are indebted to all.

KDB is deeply grateful for the opportunities, training and guidance he has received from Dr C. Derek Holdsworth, Consultant Physician at the Royal Hallamshire Hospital, Sheffield, and as a token of his appreciation dedicates this paper to him.

References

- BARDHAN, K.D. (1980). Intermittent treatment of duodenal ulcer with cimetidine. *British Medical Journal*, **281**, 20.
- BARDHAN, K.D., COLE, D.S., HAWKINS, B.W. & FRANKS, C.R. (1982). Does treatment with cimetidine extend beyond initial healing of duodenal ulcer reduce the subsequent relapse rate? *British Medical Journal*, **284**, 621.
- BARDHAN, K.D. (1984). Refractory duodenal ulcer. *Gut*, **25**, 711.
- BIANCHI PORRO, G. (1982). Long-term management of recurrent duodenal ulceration. In *Experience and innovation. A review and preview of H₂ receptor antagonists*. Program and Abstracts. World Congress of Gastroenterology, June 15, Stockholm, Sweden. Smith Kline & French International, 1982: 6.
- BIANCHI PORRO, G., BURLAND, W.L., HAWKINS, B.W. & PETRILLO, M. (1980). Long-term treatment of duodenal ulcer with cimetidine: a review. In *Further experience with H₂ receptor antagonists in peptic ulcer disease and progress in histamine research*. Torsoli, A., Lucchelli, P.E., Brimblecombe, R.W. (eds). European Symposium, Oct 18–20, 1979, Capri, Italy. p.91. Excerpta Medica: Amsterdam.
- BOYD, E.J.S., WILSON, J.A. & WORMSLEY, K.G. (1984). Safety of ranitidine maintenance treatment of duodenal ulcer. *Scandinavian Journal of Gastroenterology*, **19**, 394.
- BOYD, E.J.S., WILSON, J.A. & WORMSLEY, K.G. (1984). Recurrent ulcer disease. In *Ranitidine: therapeutic advances*. Misiewicz, J.J. & Wood, J.R. (eds). p.14. Excerpta Medica: Amsterdam.
- BURLAND, W.L., HAWKINS, B.W. & BERESFORD, J. (1980). Cimetidine treatment for the prevention of recurrence of duodenal ulcer: an international collaborative study. *Postgraduate Medical Journal*, **56**, 173.
- GEHAN, E.A. (1965). The generalised Wilcoxon test for comparing arbitrarily single-censored samples. *Biometrika*, **52**, 203.
- GOUGH, K.R., BARDHAN, K.D., CROWE, J.P., KORMAN, M.G., LEE, F.I., REED, P.I. & SMITH, R.N. (1984). Ranitidine and cimetidine in prevention of duodenal ulcer relapse. *Lancet*, **ii**, 659.
- GRAY, G.R., McWHINNIE, D., SMITH, I.S. & GILLESPIE, G. (1982). Five-year study of cimetidine or surgery for severe duodenal ulcer dyspepsia. *Lancet*, **i**, 787.
- KRATOCHVIL, P. & BRANDSTÄTTER, G. (1983). Ergebnisse einer zweijährigen Langzeitprophylaxe des Ulcus duodeni mit Cimetidin. *Medwelt*, **34**, 1380.
- McCARTHY, D.M. (1984). Smoking and ulcers – time to quit. *New England Journal of Medicine*, **311**, 726.
- MISIEWICZ, J.J. & BRADBURY, J.E. (1984). Review of trials of maintenance treatment for the prevention of duodenal ulcer recurrence. In *Ranitidine: Therapeutic Advances*, Misiewicz, J.J. & Wood, J.R. (eds). p.43. Excerpta Medica: Amsterdam.
- SCHUTZ, E. (1985). Langzeiter fahrungen mit dem neuen H₂ Blocker Ranitidin bei Patienten mit chronischer Ulcus duodeni-Erkrankung. *Kassenarzt*, **23**, 46.
- SONTAG, S., GRAHAM, D.Y., BELSITO, A. and members of Study Group (1984). Cimetidine, cigarette smoking, and recurrence of duodenal ulcer. *New England Journal of Medicine*, **311**, 689.
- STRÖM, M., BODEMAR, G., LINDHAGEN, J., SJÖHDAHL R. & WALAN, A. (1984). Cimetidine or parietal-cell vagotomy in patients with juxta pyloric ulcers. *Lancet*, **ii**, 894.
- WALAN, A., BIANCHI PORRO, G. & HENTSCHEL, E. (1985). Maintenance cimetidine for up to three years. *Lancet*, **i**, 115.