

PAPERS

Erosive oesophagitis: outcome of repeated long term maintenance treatment with low dose omeprazole 10 mg or placebo

K D Bardhan, P Cherian, A Vaishnavi, R B Jones, M Thompson, P Morris, A Brooks, J D'Silva, K R W Gillon, C Wason, J Patterson, J Polak, A Bishop

Abstract

Aims—To investigate the efficacy of daily maintenance treatment with omeprazole 10 mg in reducing the relapse rate of healed erosive oesophagitis.

Methods—Three hundred patients with erosive oesophagitis (grade 2 or greater) received omeprazole 20 mg daily for 12 weeks, followed by 40 mg daily for a further 12 weeks if required. After healing, patients were randomised to double blind treatment with omeprazole 10 mg daily or placebo for up to 18 months. On relapse the treatment cycle was repeated.

Results—The cumulative healing rate at 12 weeks in the initial healing period was 95%, and 96% and 98% on rehealing courses after relapse in the first and second maintenance periods respectively. After 12 weeks of treatment, 98% of patients were free from heartburn and 97% were free of all reflux related symptoms. Relapse in the subgroup of patients who relapsed in both maintenance periods was infrequent on omeprazole 20 mg daily: only 9% at two years. Gastrin concentrations rose above normal in one third of patients. One patient had linear hyperplasia of endocrine cells and another had micronodular hyperplasia. There were no side effects definitely attributable to omeprazole.

Conclusion—Maintenance treatment with omeprazole 10 mg daily keeps about 60% of patients with erosive oesophagitis in prolonged remission. Patients relapsing once are likely to do so again; they can subsequently be treated effectively with omeprazole 20 mg daily.

(Gut 1998;43:458-464)

Keywords: erosive oesophagitis; long term maintenance treatment; omeprazole

a dose of 20 mg daily. Clinical trials suggested that omeprazole 20 mg was the optimal dose for maintenance treatment. Analogous to the situation with the treatment of duodenal ulcer patients, it seemed possible that a lower dose would suffice for many patients with reflux oesophagitis. Thus, the aim of this study was to examine the efficacy of omeprazole 10 mg daily in maintaining remission in patients with reflux oesophagitis. Furthermore, repeat treatment with the same dose after a relapse might prove effective.

Methods

PATIENTS

Patients referred by their general practitioner for endoscopic investigation of reflux-like symptoms were invited to participate in the study. We have a long standing interest in upper gastrointestinal disease and patients referred promptly undergo endoscopy through the open access scheme (which has been running since 1976). Consequently, the population studied more closely resembles that seen in primary care—they were not referred specifically because their management was difficult.

Patients with erosive oesophagitis of grade 2 or greater (but excluding strictures), proved by endoscopy, were included in the study (see table 1 for grading). The following groups of patients were excluded: concomitant duodenal (DU) or gastric ulcers (GU) (three patients on placebo developed DU and were subsequently withdrawn); age less than 18; pregnancy, lactation, or women planning pregnancy; oesophagitis unresponsive to at least three months treatment with H₂ receptor antagonists (cimetidine \geq 1.6 g daily or ranitidine \geq 0.45 g); suspicion of upper gastrointestinal malignancy; significant associated cardiovascular, renal, or liver disease; alcoholism; concomitant phenytoin or warfarin treatments; or known poor compliance.

DRUG TREATMENT AND DESIGN OF STUDY

Figure 1 presents a flow chart of the study design.

Initial healing treatment

All patients were treated with open label omeprazole 20 mg daily (each morning) for 12

Rotherham General Hospitals NHS Trust, Rotherham

K D Bardhan
P Cherian
A Vaishnavi
R B Jones
M Thompson
P Morris
A Brooks
J D'Silva

Astra Clinical Research Unit, Edinburgh

K R W Gillon
C Wason
J Patterson

Royal Postgraduate Medical School, Hammersmith Hospital, London, UK

J Polak
A Bishop

Correspondence to:
Dr K D Bardhan,
Rotherham General
Hospitals NHS Trust,
Moorgate Road,
Rotherham S60 2UD, UK.

Accepted for publication
16 April 1998

The optimal long term medical management of reflux oesophagitis remains debatable. When this study was designed, omeprazole was available only for use in clinical trials and long term treatment was confined to patients with severe disease on compassionate grounds and only at

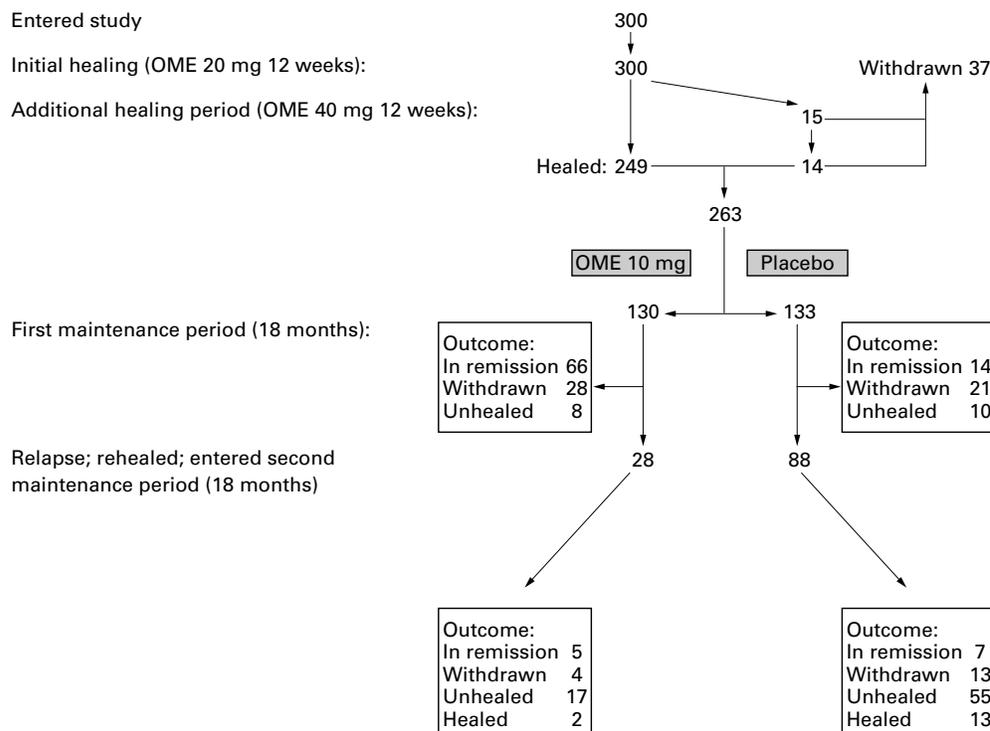


Figure 1 Flow chart of study design showing numbers of patients in the different phases, and the principal outcomes. OME, omeprazole.

weeks even if their oesophagitis had healed at an earlier stage. Those patients with persistent active disease at the end of this period had a further 12 weeks' (weeks 13–24) treatment at an increased dose of omeprazole (40 mg each morning). The few patients with disease still active after 24 weeks of treatment were withdrawn from the study at this stage.

First maintenance treatment period

Patients with disease healed at 12 or 24 weeks were randomly allocated to double blind maintenance treatment with either omeprazole 10 mg daily or identical placebo for up to 18 months. Treatment was allocated from a computer generated randomisation list. Patient treatment packs were identifiable by patient number only and neither the investigators nor the patients were aware of the treatment allocation.

Second maintenance treatment period

Patients who relapsed during the first maintenance period received a second healing course at the dose at which they had healed previously, followed by their earlier blinded maintenance treatment (omeprazole 10 mg daily or placebo) for a further 18 months.

Continuation treatment

All patients who relapsed twice were rehealed and put on open maintenance treatment with omeprazole 20 mg daily. This treatment continues.

ASSESSMENTS

Endoscopy and clinical assessments

During the initial healing phase clinical assessment and endoscopy were performed every four weeks whenever possible and always at

week 12 (or week 24 if healing treatment was extended). During maintenance treatment, patients were reviewed every three months and underwent endoscopy every six months if they were asymptomatic, or whenever symptoms recurred.

Symptomatology

At each visit an assessment was made of symptoms, specifically heartburn, epigastric pain, regurgitation, dysphagia, and odynophagia. Each symptom was graded from 0 (nil) to 3 (severe).

Definitions

Healing was defined by endoscopy and clinical assessment: disappearance of lesions (the mucosa now being entirely normal or congested but intact) and asymptomatic or having no more than mild symptoms. A relapse was defined as the recurrence of erosive changes of grade 2 or more and/or severe symptoms (grade 3) or an increase in symptoms of two grades from the previous visit. Thus, relapse could be symptomatic, with or without mucosal changes, or silent (erosive oesophagitis alone).

Adverse events

At each visit patients were asked if they had become aware of any unusual symptoms since their last visit. All such events were recorded.

Endocrine cell studies and gastrin assessment

Whenever possible, biopsy specimens were taken at each endoscopy from the corpus for endocrine cell quantification and blood was taken for gastrin estimation. Standard staining and quantification methods were used to assess

Table 1 Patients' demographic details

		Placebo	Omeprazole (10 mg)	Total
Total no of patients	n	150	150	300
Age (y)	n	150	150	150
	Missing	0	0	0
	Mean	53.5	54.8	54.1
	SD	14.7	14.1	14.4
Sex				
	n	103	103	206
Female	n	47	47	94
Body mass index				
	n	100	102	202
	Missing	3	1	4
	Mean	26.2	26.1	26.2
Male	SD	4.0	3.1	3.6
	n	45	43	88
	Missing	2	4	6
	Mean	28.1	26.5	27.3
Female	SD	4.3	4.0	4.2
Ethnic origin				
	n	150	147	297
Caucasian	n	0	3	3
Other				
	n	107	108	215
Smoking				
	n	43	43	85
Alcohol Consumption				
	n	41	53	94
No	n	109	97	206
Yes				
	n	106	94	200
Duration of reflux history (y)	Missing*	44	56	100
	Mean	2.6	2.9	2.7
	SD	3.9	4.0	4.0
	n	148	150	298
Duration of current symptoms (m)	Missing	2	0	2
	Mean	7.7	7.8	7.8
	SD	9.1	9.6	9.3
	n	77	69	146
On H ₂ receptor antagonist at time of entry to study				
	n	75	62	137
	n	57	65	122
	n	18	23	41
Grade of oesophagitis†				
	n	75	62	137
	n	57	65	122
	n	18	23	41

*In most of these patients, reasonably accurate information could not be obtained.

†Oesophagitis grading scale (Maratka³⁰): 0, normal oesophageal mucosa, no abnormalities noted; 1, no macroscopic erosions visible, mucosa is erythematous, oedema causes accentuated folds; 2, isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds but not involving the whole circumference; 3, confluent erosions involving the entire circumference of superficial ulceration; 4, erosions as described above plus deep ulceration.

Table 2 Reasons for patient withdrawal from the study

Reason for discontinuation	No of patients	
	Placebo	Omeprazole (10 mg)
Adverse event	18	12
Lost to follow up	13	19
Non-compliance with treatment	11	8
Protocol violation	2	5
Lack of efficacy	1	0
Total	45	44

overall endocrine cell density and ECL, D, and EC cell counts.¹⁻³ The total endocrine cell population was quantified using chromogranin A stain antibody which is a general endocrine cell marker. Subpopulations—for example, D cells (somatostatin) and ECL cells (serotonin),

Table 3 Cumulative healing rates on omeprazole (all patients treated analysis)

Treatment course	Week		
	4	8	12
Initial healing period (20 mg)	230/300 (77%) (72.2, 81.8)	262/300 (87%) (83.2, 90.8)	285/300 (95%) (92.5, 97.5)
Extension of initial healing period (40 mg)	9/14 (64%) (35.1, 87.2)	11/14 (79%) (49.2, 95.3)	13/14 (93%) (66.1, 99.8)
First reheel course	99/134 (74%) (66.6, 81.4)	112/134 (84%) (77.8, 90.2)	128/134 (96%) (97.2, 99.3)
Second reheel course	68/87 (78%) (68.0, 86.3)	76/87 (87%) (78.5, 93.5)	85/87 (98%) (91.9, 99.7)

Results are expressed as number (%) of patients (95% confidence intervals).

were stained separately and counted. The method of classification described by Solcia *et al* was used.⁴ The median cell count taken from all biopsy specimens at each visit provided a summary measure. Gastrin was measured according to methods previously described.⁵

STATISTICAL METHODS

The primary outcome measure was relapse rate, analysed by life table methods.⁶ A Cox proportional hazards regression model was used to assess the effect of prognostic factors on outcome. Descriptive statistics have been used elsewhere. All patients treated (APT) and per protocol (PP) analyses were done. The results from these analyses were very similar, therefore only the APT results are reported.

The treatment code was broken only after the last patient completed the study and after the complete study data were verified.

ETHICS

The study was approved by the Ethics Committee and informed written consent was obtained from each patient.

Results

Three hundred patients were entered into this study; fig 1 shows their subsequent inclusion in the various treatment periods. Table 1 shows the demographic features. Table 2 details the patients lost to follow up.

HEALING

The cumulative healing rates in the initial healing period on omeprazole 20 mg daily were: 77% at four weeks; 87% at eight weeks; and 95% at 12 weeks (table 3). Fourteen of 15 patients unhealed after 12 weeks received omeprazole 40 mg daily for a further 12 weeks; 13 healed at the end of this period (table 3). The outcome of rehealing treatment after relapse in the maintenance periods was similar to that of the initial healing period (table 3). Thus, repeated courses of omeprazole for healing remain effective.

FACTORS AFFECTING HEALING

The grade of oesophagitis at entry did not significantly affect healing rates and they were not affected if the patient had relapsed on placebo or omeprazole 10 mg (table 4).

SYMPTOM RELIEF

The cumulative proportions of patients who were free from heartburn were: 95% at four weeks; 98% at eight weeks; and 98% at 12

Table 4 Healing and grade of reflux oesophagitis

Healed at week:	4	8	12
Grade of oesophagitis			
2	107/137 (78%) (71.1, 84.9)	122/137 (94%) (90.0, 98.0)	130/137 (95%) (91.4, 98.6)
3	91/122 (75%) (67.3, 82.7)	103/122 (84%) (77.5, 90.5)	116/122 (95%) (91.1, 98.9)
4	32/41 (78%) (62.4, 89.4)	37/41 (90%) (76.9, 97.3)	39/41 (95%) (83.5, 99.4)

Results are expressed as number (%) of patients (95% confidence intervals).

weeks. Freedom from all symptoms was achieved in 91%, 96%, and 97% of patients respectively.

OUTCOME OF FIRST COURSE OF MAINTENANCE TREATMENT

The analysis of outcome of the first course of maintenance treatment is based on 263 patients. This includes 258 with healed reflux oesophagitis and five with disease still active. These five patients should have been withdrawn but in error remained in the study. Statistical correctness requires the latter five patients to be included in the analysis and to be viewed as having relapsed at day 0 of follow up. One hundred and thirty patients were assigned to omeprazole 10 mg daily and 133 to placebo. There was a notable and significant difference in outcome, the probability of continuing in remission at 18 months being 60% on omeprazole 10 mg but only 15% on placebo ($p < 0.0001$, log rank test) (fig 2). Earlier remission rates were: at six months, 82% for omeprazole 10 mg and 45% for placebo; and at 12 months, 66% and 25% respectively. Thus, relapses on placebo were frequent and early.

Recurrence of symptoms alone without endoscopic changes was the most common type of relapse and this was similar in both treatment groups (placebo 56% versus omeprazole 10 mg 53%). Relapses due to erosive oesophagitis with symptoms (26% versus 20%) were equally common, but there was an indication that silent disease occurred more frequently, though not significantly, in the omeprazole 10 mg group (18% versus 27%).

FACTORS AFFECTING RELAPSE

The grade of oesophagitis (before healing treatment), rate of healing, smoking, and alco-

hol consumption did not affect relapse rates, either on placebo or on maintenance treatment with omeprazole 10 mg.

OUTCOME OF SECOND COURSE OF MAINTENANCE TREATMENT

Repeat maintenance treatment appeared to be less successful compared with the first maintenance course, the probability of remission at 18 months being only 21% for omeprazole 10 mg and 9% on placebo, although the difference between the two groups was still statistically significant ($p = 0.016$; fig 3). However the patients who had relapsed in the first maintenance period did so again, and rapidly. This is shown by comparing the outcome of the first and second courses of maintenance treatment for patients who relapsed twice. The majority of these patients had relapsed by six months in both maintenance periods, both on placebo (87% in period 1 versus 84% in period 2), and omeprazole 10 mg (71% in period 1 versus 64% in period 2). Thus, patients who are unlikely to do well on maintenance treatment with omeprazole 10 mg are identifiable early on and repeating the same treatment does not improve the results.

OUTCOME OF OPEN MAINTENANCE TREATMENT WITH OMEPRAZOLE 20 MG

One hundred and eighteen patients received open maintenance treatment with omeprazole 20 mg daily having relapsed twice either on placebo or on omeprazole 10 mg daily. Only 10 (9%) patients relapsed by 24 months. The cumulative relapse rate was: 3% at six months ($n = 3$); 3% at 12 months ($n = 4$); and 8% at 18 months ($n = 9$). Thus, when low dose omeprazole fails, omeprazole 20 mg daily keeps most patients in remission.

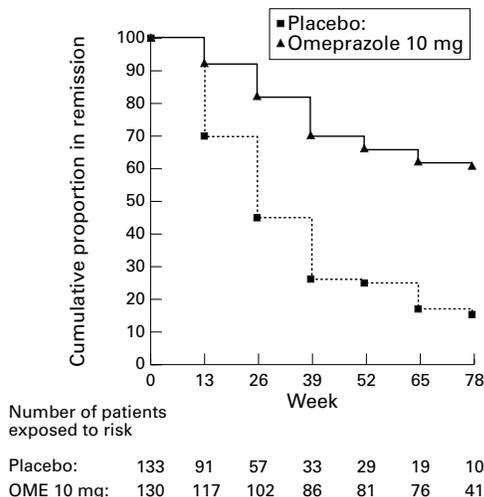


Figure 2 Proportions of patients continuing in remission on omeprazole (OME) 10 mg ($n = 130$) and placebo ($n = 133$) in the first maintenance course.

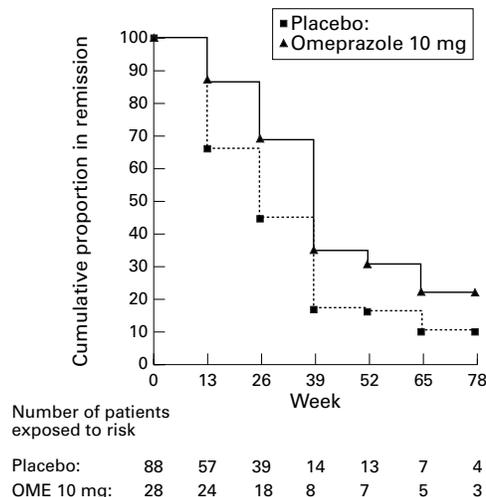


Figure 3 Proportions of patients continuing in remission on omeprazole (OME) 10 mg ($n = 28$) and placebo ($n = 88$) in the second maintenance course.

Table 5 Serum gastrin concentrations

Measurement at:	Treatment	No of patients	Mean (95% CI) (pmol/l)	No within normal range*	No above normal range*
Baseline	Placebo	47	21 (13.3, 28.7)	40	7
	Omeprazole 10 mg	49	13 (10.5, 15.5)	48	1
End of initial healing period	Placebo	127	44 (35.0, 53.0)	80	47
	Omeprazole 10 mg	131	45 (37.3, 52.7)	82	49
End of first maintenance period	Placebo	68	14 (10.2, 17.8)	66	2
	Omeprazole 10 mg	103	41 (31.7, 50.3)	72	31
End of reheat	Placebo	84	55 (43.2, 66.8)	46	38
	Omeprazole 10 mg	34	47 (31.9, 62.1)	20	14
End of second maintenance period	Placebo	46	9 (7.28, 10.72)	46	0
	Omeprazole 10 mg	21	38 (20.9, 55.1)	14	7

*Normal range: <40 pmol/l.

SERUM GASTRIN

Gastrin concentrations could be measured only in a proportion of patients. The concentrations were normal in most at entry to the study (less than 40 pmol/l; table 5). These values rose to above normal in approximately one third of patients by the end of the initial healing period with omeprazole 20 mg. Subsequently gastrin concentrations returned to normal on maintenance with placebo in all except two patients whereas they were above normal in about one third of patients on maintenance omeprazole 10 mg. The pattern repeated itself on the second healing and maintenance treatment courses.

The highest gastrin concentration recorded on healing treatment was 299 pmol/l, and in 3% of patients exceeded four times the upper limit of normal. The corresponding value on maintenance omeprazole 10 mg was 259 pmol/l (in 5%, concentrations exceeded four times the upper limit of normal).

ENDOCRINE CELL QUANTIFICATION

Unlike gastrin, there is no widely accepted normal value for endocrine cell counts. Counts on treatment were therefore compared against those at entry. Serial biopsy specimens were available only in a proportion of patients. There was no significant change in total ECL density either during healing treatment with omeprazole 20 mg or in subsequent maintenance treatment with omeprazole 10 mg or placebo (table 6). Similarly, no significant change was seen over time with D cells or EC cells. Only two of 5791 biopsy specimens showed endocrine cell hyperplasia; one patient had linear hyperplasia at the end of the second healing treatment (omeprazole 20 mg) and the other, micronodular hyperplasia after 18 months maintenance treatment with omeprazole 10 mg.

Table 6 Endocrine cell counts

Cell type	Measurement at:	Mean cell count/visual field (95% CI)			
		n	Omeprazole	n	Placebo
Total endocrine cells (chromogranin)	Baseline	88	22 (18.7, 25.3)	78	23 (19.2, 26.8)
	End initial healing	138	23 (20.5, 25.5)	140	24 (21.4, 26.7)
	End first maintenance	103	19 (16.9, 21.1)	82	19 (16.2, 21.8)
Serotonin	Baseline	86	1.2 (0.9, 1.5)	77	1.4 (1.1, 1.7)
	End initial healing	140	1.0 (0.8, 1.2)	140	1.0 (0.83, 1.17)
	End first maintenance	103	0.8 (0.65, 0.95)	82	0.9 (0.71, 1.09)
Somatostatin	Baseline	87	2.9 (2.3, 3.5)	77	3.5 (2.7, 4.3)
	End initial healing	140	2.8 (2.4, 3.2)	140	3.0 (2.5, 3.5)
	End first maintenance	103	2.4 (2.1, 2.8)	82	2.7 (2.3, 3.1)

ADVERSE EVENTS

Thirty four patients had 40 serious adverse events. These occurred on placebo (n=14), omeprazole 10 mg (n=11), omeprazole 20 mg (n=14), and omeprazole 40 mg (n=1). Most serious adverse events were unconnected with reflux disease (for example, myocardial infarction, stroke, or worsening chronic obstructive airways disease). One patient (on omeprazole 20 mg) was found to have a carcinoma of the oesophagus on repeat biopsy examinations during the first healing course. No pattern of serious adverse events emerged and the investigator reported none due to treatment.

Discussion

Our study shows that about 60% of patients with healed erosive oesophagitis can be kept in prolonged symptomatic and endoscopic remission (at least 18 months) on low dose maintenance treatment with omeprazole 10 mg daily. Repeating the treatment appears to be less successful. However, it is difficult to compare the two life table curves as the patient populations are different: those patients in remission at the end of the first 18 month maintenance period left the study at that point. A higher risk group remained and this probably explains the higher relapse rates during the second maintenance period. Most patients who relapsed in the first maintenance period relapsed again, and did so early. The majority (more than 90%) of such patients, however, could be kept in remission successfully on a higher maintenance dose of omeprazole 20 mg daily. Maintenance treatment with omeprazole 20 mg has previously been shown to be significantly more effective than omeprazole 10 mg in preventing relapse in patients with gastro-oesophageal reflux disease.⁷ This may be due to the lower variability in response to therapy during treatment with omeprazole 20 mg than with 10 mg.^{8,9}

These findings have a bearing on practical management as the appropriate dose for an individual can be determined by titration. Unless the oesophagitis is severe—for example, with deep ulcers or stricture, we suggest starting maintenance treatment with 10 mg, and increasing to 20 mg for the minority who relapse.

Early pharmacological studies showed that omeprazole 20 mg reduced 24 hour gastric acidity by about 90%^{8 10} whereas the 10 mg dose reduced acidity by about 37%. There was, therefore, reluctance in investigating the low dose for maintenance therapy in oesophagitis, particularly as early clinical trials showed high relapse rates off therapy—for example, 85% at six months.^{11 12} Our experience, however, shows that the 10 mg dose for maintenance is effective in more than half the patients. This benefit is unlikely to be the result of fortuitously selecting patients with milder disease for all had erosive changes at the start, the proportions with moderate and severe oesophagitis being similar to those reported in other series, and relapse on placebo was high confirming the aggressive nature of the problem.

Our findings are similar to recent reports on the use of maintenance omeprazole 10 mg daily in erosive oesophagitis. Hallerback *et al*¹³ reported relapse rates of 38% on omeprazole 10 mg daily compared with 28% on 20 mg daily at one year; Bate *et al*¹⁴ reported relapse rates of 50% and 26% on 10 and 20 mg respectively (and 86% on placebo). In both studies patients were treated in parallel arms and not sequentially as in ours. Laurent *et al*¹⁵ observed a symptomatic relapse rate of 10% on omeprazole 10 mg daily at six months. Somewhat higher relapse rates were reported by Laursen and colleagues⁷: 65% with omeprazole 10 mg at six months, although grade 1 oesophagitis was included in the definition of relapse in this study, unlike the majority of reported trials in this area.

Two further observations concerning the outcome of treatment in our study need comment. Firstly, the severity of oesophagitis at entry did not affect either the rate of healing or the relapse rate. This was a surprising finding in the light of other reports, including a recent meta-analysis of prognostic factors for remaining in remission.¹⁶ As the entry criteria to our and previous studies were similar, we are unable to suggest why our results are not in agreement. However, some other reported studies have also not found an association between risk of relapse and pre-entry grade of oesophagitis.^{13 17 18}

Secondly, half of the relapses were symptomatic only and without erosive changes even though all had erosive oesophagitis at entry. A further one quarter were asymptomatic but had erosive disease. These findings could influence practical management. A common approach is simply to keep patients symptom-free. There is no consensus whether silent disease should be sought out and treated. In day to day practice, therefore, maintenance therapy can be managed clinically, the dose being

titrated according to symptoms, thus avoiding routine serial check endoscopy.

Prolonged omeprazole treatment proved safe. Serious adverse events were unrelated to drug treatment.

The mean gastrin concentrations rose as expected and in one third were elevated above the upper limit of normal (<40 pmol/l) on both omeprazole 20 mg given for healing and on maintenance omeprazole 10 mg daily. Few had concentrations greater than 160 pmol/l. Reassuringly, there was no significant endocrine cell hyperplasia during this long period of follow up. Other studies which have investigated endocrine cell density changes on prolonged omeprazole treatment noted only mild changes but no carcinoids. For example, Lamberts *et al*¹⁹ showed that long term omeprazole therapy given for up to five years resulted in moderate hypergastrinaemia, and some argyrophil cell hyperplasia but no tumour. These changes correlated with the severity of corpus gastritis. Diebold *et al*²⁰ observed no difference in the ECL cell density between patients on maintenance omeprazole or H₂ receptor antagonists. Many of the patients in these series had high dose omeprazole treatment yet little endocrine cell changes were seen. By inference therefore, it is unlikely that prolonged treatment with omeprazole 10 mg daily will cause significant endocrine cell changes. Indeed, short treatment courses with omeprazole 10 mg appear to have no significant effect on plasma gastrin concentration.^{21–23}

In conclusion, omeprazole 10 mg daily is effective in maintaining prolonged remission in about 60% of patients with healed erosive oesophagitis. Those who relapse can then usually be successfully treated in the long term with omeprazole 20 mg daily.

This work was presented as a poster at the American Gastroenterological Association meeting, May 1995 (*Gastroenterology* 1995;108:A788). The work was supported by the Astra Clinical Research Unit, Edinburgh, UK.

- 1 Facer P, Bishop AE, Lloyd RV, *et al*. Chromogranin: a newly organised marker for endocrine cells of the human gastrointestinal tract. *Gastroenterology* 1985;89:1366–73.
- 2 Grimelius L. A silver nitrate stain for A2 cells in human pancreatic islets. *Acta Soc Med Upsal* 1968;73:243–70.
- 3 Sevier AC, Munger BC. A silver method for paraffin of neural tissue. *J Neuropathol Exp Neurol* 1965;24:130–5.
- 4 Solcia E, Bordi C, Creutzfeldt W, *et al*. Histopathological classification of non-antral gastric endocrine growths in man. *Digestion* 1988;41:185–200.
- 5 Briant MG, Adrian TE. Gastrin. In: Bloom SR, Long RG, eds. *Radio-immunoassay of gut regulatory peptides*. London: WB Saunders, 1982:51–9.
- 6 Collet D. *Modelling survival data in medical research*. London: Chapman and Hall, 1994.
- 6a Maratka Z. Terminology, definitions and diagnostic criteria in digestive endoscopy. *Scand J Gastroenterol* 1984;19(suppl 103):1–74.
- 7 Staerk Laursen L, Havelund T, Bondesen S, *et al*. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomised dose-finding study. *Scand J Gastroenterol* 1995;30:839–46.
- 8 Sharma BK, Walt RP, Pounder RE, *et al*. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 1984;25:957–64.
- 9 McLauchlan G, Crean GP, McColl KEL. Effect of low-dose omeprazole on gastric acid secretion in duodenal ulcer patients. *Aliment Pharmacol Ther* 1988;2:263–8.
- 10 Naesdal J, Bodemar G, Walan A. Effect of omeprazole, a substituted benzimidazole, on 24h intragastric acidity in patients with peptic ulcer disease. *Scand J Gastroenterol* 1984;19:916–22.
- 11 Bardhan K D. Omeprazole in the treatment of gastro-oesophageal reflux disease. In: Scarpignato C. Advances in drug therapy of gastroesophageal reflux disease. *Front Gastrointestinal Res* 1992;20:246–306.

- 12 Sandmark S, Carlsson R, Fausa O, et al. Omeprazole or ranitidine in the treatment of reflux esophagitis. *Scand J Gastroenterol* 1988;23:625-32.
- 13 Hallerbäck B, Unge P, Carling L, et al, and the Scandinavian Clinics for United Research Group. Omeprazole or ranitidine in long-term treatment of reflux esophagitis. *Gastroenterology* 1994;107:1305-11.
- 14 Bate CM, Booth SN, Crowe JP, et al and the SOLO investigator group. Omeprazole 10 mg or 20 mg once daily in the prevention of recurrence of reflux esophagitis. *Gut* 1995;36:492-8.
- 15 Laurent J, Cassan P, Rey JF, et al. Efficacy of omeprazole 20mg followed by maintenance treatment with omeprazole 10mg for the relief and prophylaxis against recurrence of GERD symptoms in patients with low grade esophagitis [abstract]. *Gastroenterology* 1995;108:A145.
- 16 Carlsson R, Galmiche J-P, Dent J, et al. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997; 11:473-82.
- 17 Lundell L, Backman L, Ekström P, et al. Prevention of relapse of reflux esophagitis after endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine. *Scand J Gastroenterol* 1991;26:248-56.
- 18 Hetzel DJ, Carlsson R, Dent J, et al. Relapse of esophagitis after endoscopic healing: an analysis of unfavourable prognostic factors. *Scand J Gastroenterol* 1989;24(suppl 166): A175.
- 19 Lamberts R, Creutzfeldt W, Strüber HG, et al. Long term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth and gastritis. *Gastroenterology* 1993; 104:1356-70.
- 20 Diebold MD, Richardson S, Zeitoun P, et al, and colleagues in 52 centres. Influence of the degree of severity of fundic gastritis on serum gastrin concentration and ECL cell density in controls and during prolonged treatment with antisecretory drugs [abstract]. *Gastroenterology* 1995;108: A83.
- 21 Howden CW, Derodra JK, Burget DW, et al. Effects of low dose omeprazole on gastric secretion and plasma gastrin in patients with healed duodenal ulcer. *Hepato-gastroenterology* 1986;33:267-70.
- 22 Hemery P, Galmiche J-P, Roze C, et al. Low dose omeprazole effects on gastric acid secretion in normal man. *Gastroenterol Clin Biol* 1987;11:148-53.
- 23 Prichard PJ, Yeomans ND, Shulkes A, et al. The effect of omeprazole on 24 hour intragastric pH and fasting plasma gastrin during low dosage (10 mg) in the morning or the evening. *J Gastroenterol Hepatol* 1986;1:289-95.