

Omeprazole 10 mg or 20 mg once daily in the prevention of recurrence of reflux oesophagitis

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Abstract

This study determined the optimal maintenance dose of omeprazole in reflux oesophagitis. One hundred and ninety three patients rendered asymptomatic and healed after four or eight weeks omeprazole were randomised double blind to 10 mg omeprazole once daily (n=60 evaluable), 20 mg omeprazole once daily (n=68), or placebo (n=62) for one year or until symptomatic relapse. Each omeprazole regimen was superior to placebo in preventing both symptomatic relapse (life table analysis, $p<0.001$) and endoscopically verified relapse ($p<0.001$). At 12 months, the life table endoscopic remission rates (proportions of patients without grade ≥ 2 oesophagitis) were: 50% (95% confidence intervals 34 to 66%) with 10 mg omeprazole once daily, 74% (62 to 86%) with 20 mg omeprazole once daily, and 14% (2 to 26%) with placebo. At 12 months, the life table symptomatic remission rates (proportions of patients asymptomatic or with mild symptoms) were: 77% (64 to 89%) with 10 mg omeprazole once daily, 83% (73 to 93%) with 20 mg omeprazole once daily, and 34% (16 to 52%) with placebo. Both 10 mg and 20 mg omeprazole once daily were effective in prolonging the remission of reflux oesophagitis: 10 mg may be appropriate to start longterm treatment, though the existence of a dose response relation means that 20 mg once daily may be effective in patients for whom 10 mg once daily is suboptimal.

(Gut 1995; 36: 492-498)

Keywords: omeprazole, reflux oesophagitis.

Omeprazole (Losec, Astra Pharmaceuticals) 20 mg once daily is effective in the longterm treatment of reflux oesophagitis and superior to the H_2 receptor antagonist ranitidine (150 mg twice daily) in this regard.^{1,2} Treatment should normally represent the minimum drug exposure, however, which produces the greatest benefit in the greatest proportion of patients.³ Thus, there are sound reasons for evaluating 10 mg omeprazole once daily in the prevention of relapse of reflux oesophagitis in comparison with the standard dose. Preliminary, short term (six month) trials have been conducted with the 10 mg regimen, which suggest that it may be effective as prophylaxis against the recurrence of reflux oesophagitis, although the assessment of

efficacy was based solely on (disparate) endoscopic criteria.^{4,5}

This study assessed whether 10 mg omeprazole once daily would be effective in the longterm (one year) treatment of reflux oesophagitis, in comparison with 20 mg omeprazole once daily and placebo, based on both endoscopic and symptomatic recurrences.

Methods

STUDY DESIGN

One hundred and ninety three of 200 patients both healed of reflux oesophagitis and rendered asymptomatic from 313 patients who received either omeprazole 20 mg once daily for four to eight weeks, or 20 mg once daily for four weeks followed by 40 mg once daily for the second four weeks,⁶ were randomised to receive double blind either 10 mg omeprazole once daily or 20 mg omeprazole once daily or matched placebo for up to one year. The study drugs were presented as hard gelatin capsules with an opaque body, containing either omeprazole 20 mg, omeprazole 10 mg, or placebo (lactose) as enteric coated granules, with each 'treatment' being of identical appearance. Endoscopy was performed after three months, and on completion, or in the event of symptomatic relapse (for definition see below). It was considered prudent to assess whether each patient remained healed of oesophagitis after three months, as relapse may occur comparatively early during longterm treatment, and 12 weeks has been quoted as a median time to relapse.⁷

At clinic visits every three months, patients' symptoms (overall assessment, heartburn, regurgitation, dysphagia) were recorded on a four point scale (0=none, 1=mild, 2=moderate, 3=severe); the presence or absence of odynophagia, and possible adverse events were elicited in response to a standard open question. Interim (unscheduled) visits were available to any patient experiencing troublesome symptoms. Patients also completed daily diary cards for the first three months of the study to record the severity of symptoms by day and by night, and the number of tablets of alginate-antacid relief medication (Gaviscon: Reckitt & Colman; 500 mg alginic acid, 25 mg magnesium trisilicate, 100 mg dried aluminium hydroxide gel, 170 mg sodium bicarbonate. Neutralising capacity: 3.7 mmol H^+ per tablet) taken by day and by night. The primary end point for the diary card data was the absence of symptoms by day and by night.

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Accepted for publication
15 July 1994

Endoscopic relapse was defined as the recurrence of grade 2–4 oesophagitis (for grading see Table II). The finding of grade 2–4 oesophagitis on endoscopy associated with either mild or no symptoms was considered as an asymptomatic relapse. Symptomatic relapse was defined as the recurrence of gastro-oesophageal reflux disease symptoms, graded as moderate or severe.

PATIENTS

Entry criteria for the healing trial preceding this study have been reported elsewhere,⁶ the main inclusion criteria being: age 18–80 years, minimum of three months' history of symptoms of gastro-oesophageal reflux disease, and grade 2–4 reflux oesophagitis on endoscopy (for grading see Table II); the main exclusion criteria were: oesophageal varices or stricture, upper gastrointestinal bleeding, peptic ulcer, and past upper gastrointestinal surgery or vagotomy.

At entry to this maintenance study each patient had to have been rendered healed (grade 0 on endoscopy) and symptom free (grade 0 on patient's overall assessment) after their initial treatment with omeprazole. In this study, patients were withdrawn in the event of (a) the recurrence of symptoms, graded as moderate or severe, and which would in the investigator's opinion have warranted a further healing course of omeprazole; (b) erosive oesophagitis (grade 2–4) at the three month endoscopy.

All patients gave written informed consent to participate in the study, which was approved by the ethics committee at each institution.

STATISTICAL ANALYSES

In the primary analysis, the endoscopic remission rates after 12 months with omeprazole 10 mg once daily and placebo were compared, giving at least 99% power at the 5% significance value to detect the observed difference between groups of 36% (50% *v* 14%, respectively).

Endoscopic and symptomatic remission rates with 95% confidence intervals were determined using life table analyses. In addition to the full 12 month analyses, it was considered important to highlight the analyses for the first three months, as the design of the trial up to then wholly reflected routine clinical practice and patients' continuous (daily) assessments of symptoms were available from diary cards.

An additional comparison of remission rates (all patients treated approach, with denominators of 60, 10 mg omeprazole; 68, 20 mg omeprazole; 62, placebo; unless otherwise stated) was carried out (χ^2 tests), although it is recognised that this analysis may underestimate the true proportions of patients in remission, it permits comparison to be made with some earlier trials.

A logit analysis was conducted to identify possible factors predictive of a reduced risk of relapse: covariates were duration of most

recent episode of reflux oesophagitis; endoscopic grade of oesophagitis or overall symptom grading at entry into the preceding healing trial, healing treatment (omeprazole 20/20 mg or 20/40 mg) and duration required (four or eight weeks) to attain present endoscopic and symptomatic remission; age; sex; concurrent smoking or alcohol consumption; previous H₂ receptor antagonist use; and treatment (10 mg omeprazole, 20 mg omeprazole or placebo).

Plots of diary card assessments were derived from the percentage of patients reporting no daytime or night time symptoms. These data are presented cumulatively as the average number of such days per patient; and a comparison made between groups using a χ^2 test.

Values are presented as mean (SD).

Results

One hundred and ninety three patients were randomised to receive 10 mg omeprazole once daily (n=61), 20 mg omeprazole once daily (n=69), or placebo (n=63). Three patients (one omeprazole 10 mg, one omeprazole 20 mg, one placebo) were lost to follow up. In the absence of any data on efficacy, these patients were excluded from the analyses. There were no significant differences between the groups at randomisation into the study with regard to demographic characteristics, history of oesophagitis, and endoscopic findings immediately before the most recent healing treatment (Tables I and II).

ASSESSMENTS AT CLINIC VISITS

Endoscopic relapse: one to three months

At three months, the life table endoscopic remission rates (proportions of patients

TABLE I Patients' characteristics at randomisation

	Omeprazole 10 mg	Omeprazole 20 mg	Placebo
<i>Demographic features</i>			
Patients (n)	60	68	62
Sex (M:F)	44:16	48:20	48:14
Age (y)	53 (15)	53 (14)	53 (14)
Weight (kg)	78 (13)	76 (14)	80 (11)
		(n=67)	(n=61)
Height (cm)	170 (11)	171 (9)	172 (8)
	(n=59)	(n=67)	
Smokers (%)	25	22	19
Drinkers (%)	67	71	86
<i>Oesophagitis history</i>			
Years since 'oesophagitis' first diagnosed	1.2 (2.6)	1.7 (4.3)	1.2 (2.3)
	(n=52)	(n=55)	(n=56)
<i>Symptom history</i>			
Assessment immediately before most recent healing treatment			
Heartburn (%)	98	94	95
Regurgitation (%)	77	72	71
Dysphagia (%)	37	35	32
Odynophagia (%)	25	27	29
<i>Healing regimen for most recent episode*</i>			
Om 20 (%)	73	59	60
Om 20/20 mg (%)	8	13	16
Om 20/40 mg (%)	18	28	24

Data are shown as numbers or proportions of patients in each category or as mean (SD). *Patients received 20 mg omeprazole once daily for four weeks. Those not both healed and symptom free after four weeks received either 20 mg omeprazole once daily (OM 20/20 mg) or 40 mg omeprazole once daily (OM 20/40 mg) for a further four weeks (weeks 5–8).

TABLE II Findings at endoscopic examination immediately before the most recent healing treatment

	Omeprazole 10 mg	Omeprazole 20 mg	Placebo
Patients (n) with each grade of oesophagitis			
Grade 0	0	0	0
Grade 1	0	0	0
Grade 2 (%)	43 (72)	44 (65)	42 (68)
Grade 3 (%)	14 (23)	22 (32)	15 (24)
Grade 4 (%)	3 (5)	2 (3)	5 (8)
Linear extent of oesophagitis (cm)	4.5 (2.3)	4.7 (2.1)	4.4 (2.2)
Stricture passable with an adult endoscope (%)	4/60 (7)	8/68 (12)	4/62 (7)
Endoscopic evidence of Barrett's oesophagus (%)	5/60 (8)	1/68 (2)	5/62 (8)

Data are shown as numbers of patients in each category, or as mean (SD). Endoscopic grades were defined as follows: Grade 0 – normal mucosa. Grade 1 – no macroscopic erosions visible; erythema or diffusely red mucosa; oedema causing accentuated folds. Grade 2 – isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds, but not involving the entire circumference. Grade 3 – confluent erosions involving the entire circumference. Grade 4 – frank benign ulcer. Barrett's oesophagus was defined as the presence of columnar lined epithelium extending more than 3 cm above the proximal margin of the gastric folds (gastro-oesophageal junction) and around the entire circumference.

without grade ≥ 2 oesophagitis, Fig 1) were: 79% (95% CI 69 to 90%) (68% on an all patients treated basis) with omeprazole 10 mg once daily, 89% (81 to 97%) (76%) with 20 mg omeprazole once daily, and with placebo 41% (28 to 53%) (23%; 10 mg group NS *v* 20 mg group, each $p < 0.0001$ *v* placebo, Fig 2).

At the three month clinic visit, fewer patients receiving the 10 or 20 mg regimens were classified as having an asymptomatic endoscopic relapse than those receiving placebo (eight of 47 (17%) of those in symptomatic remission in the 10 mg group, seven of 58 (12%) 20 mg group, NS between groups, each $p < 0.001$ *v* 18 of 30 (60%) placebo). Of the 'asymptomatic' relapses, six of eight receiving 10 mg omeprazole, four of seven

receiving 20 mg omeprazole, and 12 of 18 receiving placebo were associated with the recurrence of mild symptoms.

Endoscopic relapse: one to 12 months

At 12 months, the life table endoscopic remission rates (Fig 1) were: 50% (95% CI 34 to 66%) (50% on an all patients treated basis) with omeprazole 10 mg once daily, 74% (62 to 86%) (68%) with 20 mg omeprazole once daily, and with placebo 14% (2 to 26%) (10%; 10 mg group NS *v* 20 mg group, each $p < 0.0001$ *v* placebo, Fig 2).

At the one year clinic visit, the proportions without troublesome symptoms but relapsing endoscopically were again similar in the omeprazole treated groups, although a statistical comparison against placebo was not possible given the small number of patients in symptomatic remission in the placebo group (five of 28 (18%) of those 'asymptomatic' in the 10 mg group, three of 39 (8%) 20 mg group, NS between groups, three of five (60%) placebo). Of the 'asymptomatic' relapses, two of five receiving 10 mg omeprazole, one of three receiving 20 mg omeprazole, and one of three receiving placebo were associated with the recurrence of mild symptoms.

Symptomatic relapse: one to three months

At three months, the life table symptomatic remission rates (proportions of patients asymptomatic or with mild symptoms, Fig 3) were: 91% (95% CI 84 to 99%) (78% on an all patients treated basis) with omeprazole 10 mg once daily, 94% (88 to 100%) (85%) with 20 mg omeprazole once daily, and with placebo 63% (55 to 76%) (48%; 10 mg group NS *v* 20 mg group, each $p < 0.001$ *v* placebo, Fig 4).

Symptomatic relapse: one to 12 months

At 12 months, the life table symptomatic remission rates (Fig 3) were: 77% (95% CI 64 to 89%) (78% on an all patients treated basis) with omeprazole 10 mg once daily, 83% (73 to 93%) (82%) with 20 mg omeprazole once daily, and with placebo 34% (16 to 52%) (45%; 10 mg group NS *v* 20 mg group, each $p < 0.0001$ *v* placebo, Fig 4).

Logit analysis

The most influential factors for a reduced likelihood of endoscopic relapse were: treatment (20 mg omeprazole > 10 mg omeprazole > placebo; $p < 0.0001$), and treatment duration required to attain present endoscopic and symptomatic remission (four or eight weeks; $p < 0.01$); with the highest probability of sustained remission being associated with longterm 20 mg omeprazole once daily, and with remission being attained after four weeks rather than eight weeks treatment of the index episode of reflux oesophagitis.

The factors most predictive of a reduced risk of symptomatic relapse were: treatment

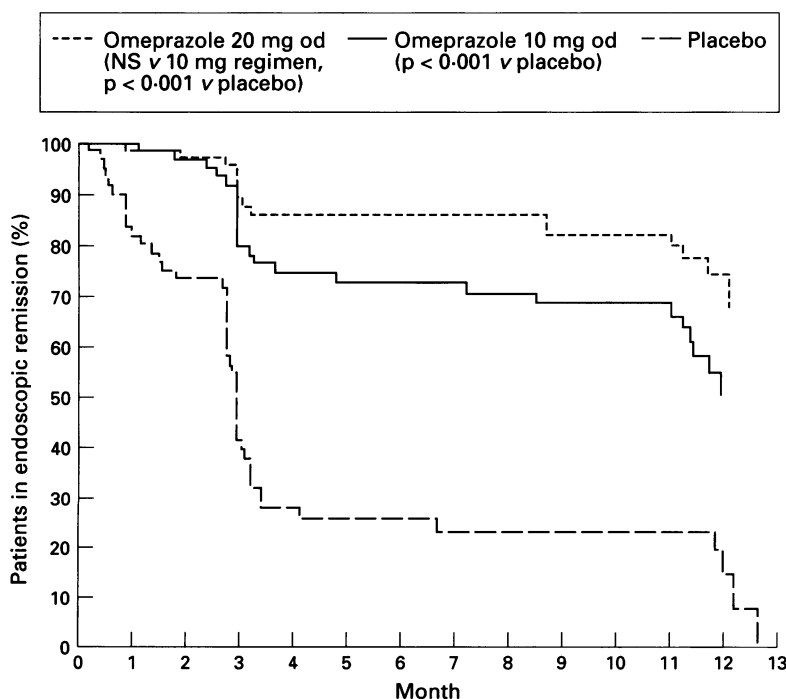


Figure 1: Endoscopic relapse: 1 to 12 months (presentation extended to day 385 to include data from temporal outliers for the endoscopy scheduled at 12 months). OD=once daily.

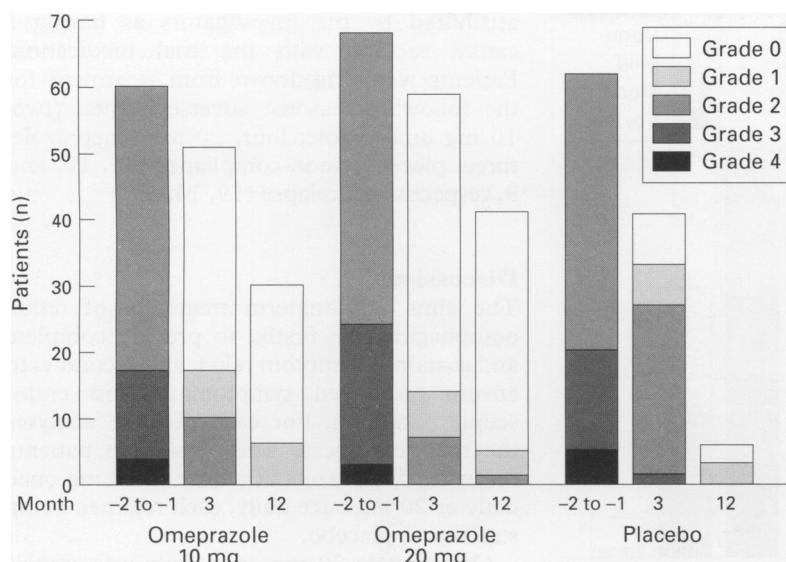


Figure 2: Endoscopic grades at entry to the preceding healing trial (-2 to -1 months), then after 3 months and 12 months maintenance treatment; NS between 10 mg and 20 mg groups after 3 and 12 months, each $p < 0.0001$ v placebo.

(20 mg omeprazole > 10 mg omeprazole > placebo, $p < 0.0001$), and overall symptom grading at entry into the preceding healing trial ($p < 0.05$); with the highest probability of sustained remission being associated with longterm 20 mg omeprazole once daily, and with the presence of mild symptoms at presentation for the preceding episode of reflux oesophagitis.

'Survival' time in study

The interval from randomisation to either withdrawal of treatment or study completion was longer in the omeprazole treated groups than the placebo group (247 days, 10 mg group; 263 days, 20 mg group; NS between groups, each $p < 0.001$ v 113 days placebo).

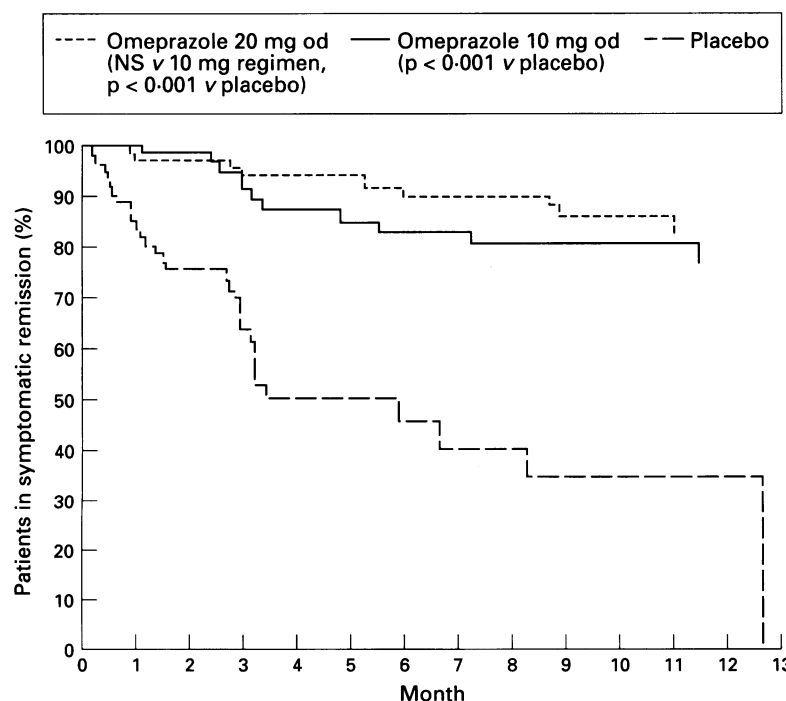


Figure 3: Symptomatic relapse: 1 to 12 months (presentation extended to day 385 to include datum from temporal outlier for the visit scheduled at 12 months).

Symptoms recorded by the physician

At three months 35 (58% on an all patients treated basis (67% of those for whom data are available)) with 10 mg once daily, 47 (69% (78%)) with 20 mg once daily, and 17 (27% (42%)) with placebo were completely asymptomatic (NS between 10 mg and 20 mg groups, each $p < 0.001$ v placebo).

The proportions of patients reported as asymptomatic on completion of the study were 32 (53% (56%)) receiving 10 mg once daily, 46 (68% (71%)) receiving 20 mg once daily, and 14 (23% (24%)) receiving placebo (NS between 10 mg and 20 mg groups, each $p < 0.001$ v placebo). Table III shows the proportions of patients without specific symptoms after three months treatment and on completion.

Diary card assessments: one to three months

Patients receiving either dose of omeprazole had more days free of symptoms than those receiving placebo (Fig 5): cumulatively, by three months on average each patient experienced 63 such days in the 10 mg group, and 65 days in the 20 mg group, compared with 45 days with placebo (NS between 10 mg and 20 mg regimens, each $p < 0.01$ v placebo). With regard to the gain in symptom free days, this represents on average during the initial three months an additional 18 or 20 days without any symptoms for each patient receiving omeprazole 10 mg once daily or 20 mg once daily, respectively, in comparison with placebo. Conversely, the probability of patients in the 10 mg and 20 mg groups experiencing a symptomatic day was 54% ($100 \times (84 - 63) / 84 - 45$) and 49% ($100 \times (84 - 65) / 84 - 45$), respectively, of that for patients receiving placebo.

Tolerability

A total of 91 adverse events was reported during the study, 33 from 19 of 61 patients receiving omeprazole 10 mg once daily, 42 from 25 of 69 patients receiving omeprazole 20 mg once daily, and 16 from 13 of 63 patients receiving placebo. The largest number of adverse events was gastrointestinal (13, 10 mg omeprazole; 12, 20 mg omeprazole; nine, placebo), for example, diarrhoea, vomiting; then in order of diminishing frequency: circulatory (10, 10 mg omeprazole; four, 20 mg omeprazole; none, placebo), for example, angina pectoris; musculoskeletal (two, 10 mg omeprazole; four, 20 mg omeprazole; three, placebo), for example, pain in the joints.

In general, the nature and incidence of adverse events were comparable across the treatment groups. With regard to circulatory adverse events, these were reported by six patients receiving 10 mg omeprazole (10 adverse events/one treatment withdrawal) by three receiving 20 mg omeprazole (4/0), and by none receiving placebo. This represents a subgroup of elderly trial patients, as the mean (SD) age of these nine patients was 69 (4) years (compared with 53 (14) years for the whole study patient population). Most

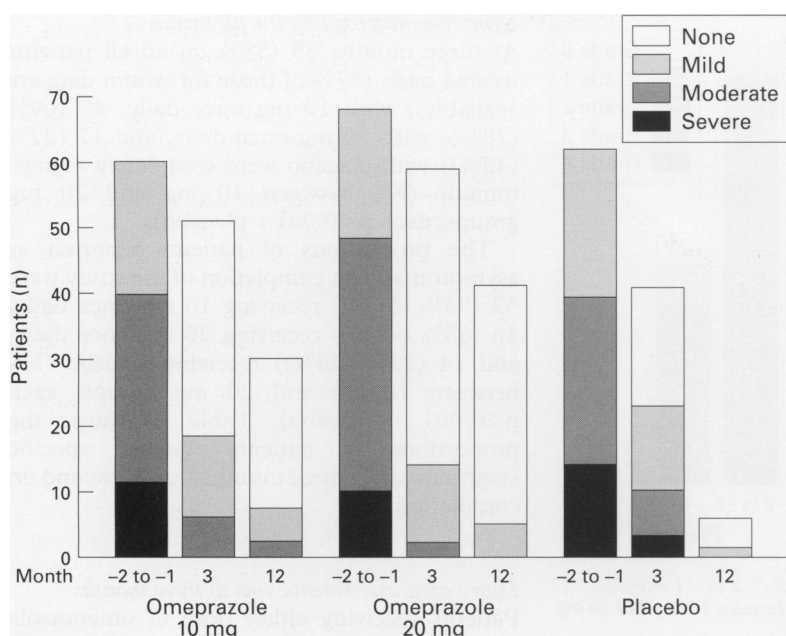


Figure 4: Symptom grades at entry to the preceding healing trial (-2 to -1 months), then after 3 months and 12 months maintenance treatment; NS between 10 mg and 20 mg groups after 3 and 12 months, each $p < 0.001$ v placebo.

(eight of 14) of the reports were of angina pectoris, and all but one of these were associated with previous (pre-trial) cardiovascular dysfunction, for example, myocardial infarction, hypertension, angina. The remaining reports were of peripheral oedema ($n=4$, three of which were associated with previous cardiovascular dysfunction), cerebrovascular disorder, and syncope. No relation between the dose of omeprazole and the incidence of circulatory adverse events was apparent, although no such events were seen in patients who received placebo. As regards outcome, nine of the adverse events resolved with continued omeprazole treatment; there being no reports of any of the remainder resolving upon withdrawal of treatment.

Seven adverse events were classified as serious according to the protocol definition, as follows: adverse events requiring hospitalisation (four, 10 mg omeprazole; one, 20 mg omeprazole; one, placebo), malignancy (one, omeprazole 20 mg; abdominal pain of sufficient severity to require treatment withdrawal, leading to a subsequent diagnosis of pancreatic carcinoma; patient died 53 days after withdrawal of treatment); none was

attributed by the investigators as having a causal relation with the trial medication. Patients were withdrawn from treatment for the following reasons: adverse events, (two, 10 mg omeprazole; four, 20 mg omeprazole; three, placebo), non-compliance (11, 10, and 9, respectively), relapse (19, 14, 45).

Discussion

The aims for longterm treatment of reflux oesophagitis are: firstly, to provide complete and sustained symptom relief; and secondly, to ensure prolonged symptomatic and endoscopic remission. For each of these analyses the rates of success were similar in patients receiving omeprazole at a dose of 10 mg once daily or 20 mg once daily, each regimen being superior to placebo.

Omeprazole 20 mg once daily was associated with a one year endoscopic remission rate of 74%, which is similar to previously published figures for this regimen (89%¹; 50%²). Though in statistical terms (in the survival analyses) the two omeprazole regimens were deemed to be of comparable efficacy in preventing both symptomatic and endoscopically verified relapse, there was consistent numerical superiority for the higher dose in each of the analyses; a trend indicative of a clinically relevant distinction between treatments. Whereas the 10 mg dose may be appropriate to start longterm treatment, the existence of a dose response relation means that a daily dose of 20 mg may be effective in patients for whom 10 mg is suboptimal.

The clinical effectiveness of omeprazole at a dose of 10 mg in this study would seem to surpass that anticipated, based on clinical pharmacology studies.⁸⁻¹⁰ We believe that this type of 'discrepancy' can be explained by the fact that many of the early studies used healthy volunteers rather than patients or involved small numbers of subjects, or both.^{8,9} Recent work considers such points, and has shown that the acid suppression achieved with 10 mg omeprazole is sufficient to produce healing in most duodenal ulcer patients.¹⁰ None the less, it seems inadvisable to extrapolate from one condition (active duodenal ulcer disease) to another (healed reflux oesophagitis) and from data on clinical pharmacology to those on clinical effectiveness, in seeking to predict patients' responsiveness to 10 mg omeprazole.

It is appropriate that clinical trials are directed at clinical end points appertaining to the 'usual' assessment of patients within the healthcare system. Initial assessments of relapse and decisions about clinical interventions in gastro-oesophageal reflux disease, are made routinely on a symptomatic basis, a practice wholly reflected by the first three months treatment within this trial. An endoscopy was scheduled after three months, as it was deemed prudent to assess whether patients remained healed of oesophagitis, a decision supported by the finding that almost one third of patients randomised to placebo, although without troublesome symptoms,

TABLE III Relief of specific symptoms recorded by physicians at clinic visits

	Omeprazole 10 mg	Omeprazole 20 mg	Placebo
Heartburn			
Month 3 (%)	40 (67 (77))†	51 (75 (85))‡	18 (29 (44))
Completion (%)	34 (57 (61))†	50 (74 (77))‡	13 (21 (22))
Regurgitation			
Month 3 (%)	43 (72 (83))*	56 (82 (93))‡	26 (42 (63))
Completion (%)	39 (65 (70))‡	55 (81 (85))‡	18 (29 (32))
Dysphagia			
Month 3 (%)	48 (80 (94))	59 (87 (100))*	38 (61 (95))
Completion (%)	52 (87 (95))	64 (94 (98))	50 (81 (86))
Odynophagia			
Month 3 (%)	52 (87 (100))*	59 (87 (98))*	40 (65 (98))
Completion (%)	54 (90 (96))	60 (88 (92))	49 (79 (84))

* $p < 0.01$, † $p < 0.001$, ‡ $p < 0.0001$ v placebo; NS between 10 mg and 20 mg groups in each assessment. Data are shown as number of patients without the symptom. Proportions are given in parentheses on the following basis: (all patients treated (of these for whom data are available)).

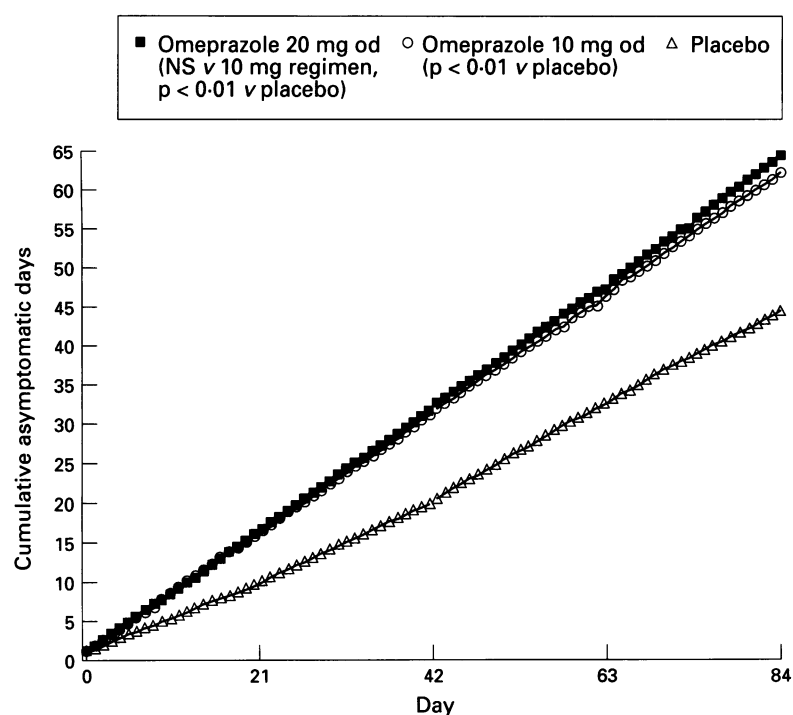


Figure 5: Cumulative number of days (of 24 hours each) free of symptoms per patient receiving 10 mg omeprazole once daily, 20 mg omeprazole once daily, or placebo; based on diary card data.

were found to have erosive oesophagitis. In contrast, this was true for only some 13% and 10% of patients receiving either 10 mg or 20 mg omeprazole, respectively, illustrating that the continued absence of troublesome symptoms is a reliable indicator of sustained endoscopic healing in patients given omeprazole. These findings support the findings of previous work, showing a positive correlation between symptom improvement and endoscopic healing in most patients treated with omeprazole.¹¹ Hence, patients receiving omeprazole are considered unlikely to require endoscopy to detect their relapse, which is an important consideration given the present high demands being placed upon finite endoscopy services, and one which could have financial attractions for a healthcare purchaser.¹²

The recurrence of even mild symptoms can be indicative of endoscopic relapse, and such patients may require longterm continuous treatment. Moreover, truly asymptomatic relapse was rare in this study. Although a higher proportion of patients receiving placebo than receiving either dose of omeprazole were regarded as treatment failures after three months and were therefore lost to follow up, the overall analysis after 12 months was consistent with that over the first three months of treatment.

Some may argue that longterm symptom relief alone is an adequate goal, but with ineffective treatment there remains the suspicion of an unacceptably high number of (unpredictable) endoscopic relapses, which could ultimately be associated with complications including the possible development of oesophageal stricture or columnar metaplasia, or both.¹¹ In clinical trials omeprazole has been shown to be effective not only in preventing the recurrence of oesophagitis but

also in oesophageal stricture prophylaxis¹³ and in inducing regression of columnar mucosa in Barrett's oesophagus,¹⁴ hence its use in the long term may reduce the incidence of gastro-oesophageal reflux disease associated complications.

Omeprazole treatment was shown, through the analysis of possible prognostic factors, to be associated with a reduced likelihood of relapse, in agreement with the results of the life table analyses. The finding of longer 'survival' times in the study of patients receiving each omeprazole regimen, more than twice the duration seen with placebo, is a composite indicator of the therapeutic advantage for omeprazole and its good tolerability.

This study reflects the maintenance treatment of patients with signs and symptoms of oesophagitis at initial presentation. Having a placebo control group offers an insight into the natural history of this chronic recurrent condition. Most patients receiving placebo relapsed within three months of attaining remission, pointing to the need for effective longterm treatment in reflux oesophagitis. A less highly selected population than that included in this trial would contain patients with typical reflux symptoms but without oesophagitis. While it is not as yet possible to predict which of these endoscopy 'negative' patients, subsequent to satisfactory initial treatment, will require no further treatment, or intermittent therapy; some will require longterm continuous treatment. In this trial, symptomatic relapse was insensitive to the initial grade of oesophagitis, whereas there was a positive correlation between the likelihood of relapse and symptom severity immediately before acute treatment. Thus, one possible inference would be that patients with troublesome symptoms of gastro-oesophageal disease but no unequivocal endoscopic evidence of oesophagitis, are at risk of relapse and hence are candidates for long term treatment.

In conclusion, omeprazole at half the standard healing dose for reflux oesophagitis is effective in long term disease treatment, by prolonging remission. Omeprazole 10 mg once daily may be used when starting maintenance treatment. Patients with an apparent clinical need for optimal treatment may have need for the higher dose, including those slow to attain remission or prone to troublesome symptoms or with a history of complication, or the few who are inadequately controlled with 10 mg.

The following physicians also contributed to the study: P B McIntyre, Queen Elizabeth II Hospital, Welwyn Garden City; R J McFarland, Ulster Hospital, Belfast; J R B Green, City General Hospital, Stoke on Trent; R P H Thompson, St Thomas' Hospital, London; J D R Rose, Ballochmyle Hospital, Ayrshire; G Bevan, Edgware General Hospital, Edgware; T K Daneshmend, Royal Devon and Exeter Hospital, Exeter; J Calam, Hammersmith Hospital, London; T O'Gorman, Regional Hospital, Galway; D N Clarke, Stirling Royal Infirmary, Stirling; D R Shreeve, North Manchester General Hospital, Manchester; K F Schiller, St Peter's District General Hospital, Chertsey; N Krasner, Walton Hospital, Liverpool; D N Foster, Birch Hill Hospital, Rochdale; P M Smith, Llandough Hospital, Penarth; M C Bateson, The General Hospital, Bishop Auckland. Emma Beresford analysed the study and Sarah Hewett prepared the manuscript.

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