

CLINICAL TRIAL

Effect of omeprazole and sucralfate on prepyloric gastric ulcer. A double blind comparative trial and one year follow up

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Abstract

This study compared healing rates, relief of symptoms, frequency of adverse events, and proportion of patients in remission after one year follow up in 104 patients with active prepyloric ulcer during treatment with 40 mg omeprazole once daily or 2 g sucralfate twice daily, using a randomised double blind controlled trial. Healing rates after two, four, and six weeks were (omeprazole/sucralfate) 49%/23%; 83%/59%; 90%/70% respectively. After two weeks, omeprazole was more efficient than sucralfate in relief of daytime and nocturnal epigastric pain, nausea, and heartburn. The proportion of patients in remission after one year follow up was significantly higher in the omeprazole group ($p < 0.01$). Of the healed patients ulcers recurred in 36% in the omeprazole group and in 46% in the sucralfate group. It is concluded that the ulcer healing rate was higher and symptom relief was more pronounced in the omeprazole group compared with the sucralfate group, and that more patients were still in remission after a one year follow up period.

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Treatment of patients with prepyloric gastric ulcer remains a therapeutic challenge. The healing rates are lower than among patients with ulcers located in duodenum and gastric body.¹⁻⁴ It is generally believed that prepyloric ulcers resemble duodenal ulcers with regard to acid secretory pattern.³ It has been found that omeprazole compared with cimetidine accelerates heal-

ing and pain relief in patients with prepyloric ulcer.⁴

Sucralfate has been shown to heal ulcers at the same rate as antacids and cimetidine.⁵⁻⁷ In patients with duodenal or gastric ulcers, omeprazole as a single dose of 20 mg daily provides more rapid and complete healing compared with ranitidine 150 mg twice daily or 300 mg at night time, or cimetidine 800 or 1000 mg/day.⁸

No trials have compared omeprazole and sucralfate. The aim of this study was to compare the effect of omeprazole (40 mg once daily) with that of sucralfate (2 g twice daily) on prepyloric ulcer healing and on ulcer symptoms. When ulcer healing had occurred, the patients were followed up for 12 months to compare the time in remission after the two treatment regimens.

Patients and methods

DESIGN AND PATIENT RECRUITMENT

The study was a multicentre, double blind, randomised trial. Outpatients from five centres were selected for the study if they fulfilled two criteria. Firstly, at least one prepyloric ulcer verified by endoscopy preferably not more than four days and definitely not more than 10 days before inclusion. The actual delay was about four days from endoscopy to start of treatment. The ulcer(s) were ≥ 5 mm and with a visual loss of substance (erosions and ulcers < 5 mm were excluded). All gastric ulcers within 2 cm from the pyloric ring were defined as prepyloric. Secondly, an ulcer history with significant symptoms for at least two months. Scheduled study days were after two weeks \pm two days, four weeks \pm two days, and after six weeks \pm two days.

EXCLUSION CRITERIA

(1) Patients below 18 or above 80 years were excluded, as were pregnant or lactating women and those who could bear children not using oral contraception or an intrauterine device. (2) Treatment with any anti-ulcer drugs in ulcer healing doses during the last week before inclusion. (3) Pyloric stenosis that necessitated surgical treatment. (4) Concurrent duodenal ulcer or gastric ulcer, or both. (5) History of gastric surgery apart from simple closure.

TABLE 1 Recruitment, loss, and withdrawal of patients distributed by treatment groups and the composition of two cohorts used in the analysis

	Omeprazole			Sucralfate				
	Entry patients (n)	Week 2	Week 4	Week 6	Entry patients (n)	Week 2	Week 4	Week 6
Recruited	53				53			
Ineligible according to entry criteria	1				1			
Evaluable 'intention to treat' cohort		52	52	52	52	52	52	52
Withdrawn or lost to follow up		1	1	1	1	3	3	3
Ineligible at single study days because of protocol violation		2	4	1	3	5	6	6
Evaluable 'per protocol' cohort		49	47	50	48	44	43	43

(6) Concurrent disease or treatment complicating the evaluation of drug, for example, known liver or kidney disease, suspicion of malignant disease(s). (7) Treatment with any non-registered investigational drug during the last four weeks before inclusion. (8) Regular treatment with salicylates or non-steroid anti-inflammatory drugs within the last four weeks before inclusion. (9) Chronic alcoholism, drug abuse or any other condition associated with poor patient compliance. (10) Patients requiring an interpreter.

TREATMENT

Two 20 mg omeprazole capsules once daily or four 500 mg sucralfate tablets twice daily were given. A double dummy technique was used. Treatment continued for two to six weeks – that is, until endoscopic healing. Symptoms were rated by diary cards (yes/no).

END POINTS

The primary end point was to compare the prepyloric ulcer healing rates during treatment with omeprazole or sucralfate. The secondary end point was to compare the relief of symptoms and frequency of adverse events during the treatment.

FOLLOW UP STUDY

Patients with healed ulcers entered a follow up study. In the one year follow up study the patients were asked to contact the clinic if ulcer like symptoms occurred for a period of three days or more within one week. Gastroscopy was done only in symptomatic patients as soon as possible. The patients were told not to take any anti-ulcer drugs, but low capacity antacids were permitted for symptomatic relief. All patients from the trial who had healed their ulcer after two, four or six weeks' treatment and who were free from ulcer symptoms were included in the analysis. Also, patients who were not healed were included and their time in remission was set to zero.

LABORATORY INVESTIGATIONS

These included haemoglobin, leucocytes, and platelets counts, serum creatinine, electrolytes, bilirubin, alkaline phosphatase, albumin, and glucose tests.

STATISTICAL CONSIDERATIONS

The endoscopy result after four weeks of treatment was chosen as the primary end point and the necessary fixed size was calculated to be about 160 patients (80 in each group: $\alpha=0.05$ (two tailed), $\beta=0.20$). The difference in healing rate between the two drugs was assumed to be 25%. Expected healing rate in the sucralfate group=0.55, and the difference not to be overlooked=0.25. To obviate inclusion of more patients than necessary, the O'Brien and Flemming procedure⁹ was applied as a stopping rule, and the results of the trial were analysed by

statisticians, independent of clinicians, when 3/5 (96) and 4/5 (128) of the patients planned for inclusion had completed four weeks' treatment. The statistical methods used were the Cochran-Mantel-Haenszel test and a standard χ^2 test. Only two tailed tests were used. Tests of healing and confidence limits of healing rates are adjusted for the interim analysis to have an overall significance value of 5%.

The primary efficacy variable was endoscopic ulcer healing and the data were subjected to both a 'per protocol analysis' – including only patients who completed an assessment period according to the protocol and an 'intention to treat analysis' – including all patients who entered the study. Patients lost to follow up were considered unhealed in the formal tests of healing when using the 'intention to treat' approach.

In the follow up study survival curves were estimated according to the lifetable method. The SAS procedure *lifetest* has been used to estimate the survival curves and the log rank test was used to compare the two treatment groups.

The variable under analysis was time in uninterrupted remission or the time to first relapse. As the follow up period was limited to 12 months, some patients would have censored follow up times. The variable takes value 0 for patients with unhealed ulcer at completion of the initial treatment course and for patients withdrawn from treatment because of worsening of symptoms or lack of effect during the first part of the study. These patients were considered to have had a relapse. Patients with healed ulcer after completion of the first part of the study, but with persistent symptoms would have their time in uninterrupted remission set to zero and considered to have had a relapse. Patients not seen during the follow up study were considered not to have experienced a relapse, but their time was also set to zero. Patients lost to follow up during the follow up study were considered not to have experienced a relapse and their time in uninterrupted remission was based on their last endoscopy day.

The analysis was based on all randomised patients, except 11 patients in the following groups: (1) patients not treated in the first part of the study, (2) patients excluded from the intention to treat analysis in the first part because of major violation of inclusion/exclusion criteria, (3) patients lost to follow up or refusing endoscopy during the first part, (4) patients withdrawn from treatment during the first part of the study because of non-compliance with the study

TABLE II Descriptive data of patients treated with omeprazole or sucralfate

	Omeprazole	Sucralfate
Sex ratio (M:F)	20:32	22:30
Mean age (y)	57.8 (19–78)	52.8 (20–79)
Mean length of history (y)	6.4 (8.0)	3.7 (6.5)*
Ratio of smokers to non-smokers	35:17	33:19
Use of alcohol (drinks/week)		
<5	42	43
>5	8	9
Ulcer size before entry (mm)		
5–10	43	41
10–20	9	7
>20	0	3
Median	8.0	8.0

* = SD.

protocol. An analysis was also made on patients only, who were healed in the first part of the study. A technical problem appeared in the survival analysis. The time of the 12 months' visit varied around day 360. Patients attending the clinic within the time interval 330–390 without relapse were considered to have completed the whole study period without relapse. Their last visit day was redefined to 361. Patients attending the clinic within the time interval day 360–390 with relapse were considered to have had a relapse within the study period. Their last visit was redefined to 359.

ETHICS

The study was approved by the local ethics committee and the Board of Health. Written and oral information was given to all patients in accordance with the rules of the Central Scientific Ethical Committees for Denmark. The study was conducted in accordance with the Helsinki declaration.

Results

DESCRIPTION AND COMPARISON OF TREATMENT GROUPS

The first interim analysis resulted in an early finish to recruitment, when a total of 106 patients had been randomised into the trial, 36 from centre 1, 20 from centre 2, 35 from centre 3, 12 from centre 4, and three from centre 5. Two patients were excluded because of violation of inclusion criteria (gastric ulcer and refusal to participate).

The critical value according to the O'Brien and Flemming procedure when 102 of 160 patients had completed the study is 6.02 (overall significance value 5%). A Mantel-Haenszel test stratified by centre and using an intention to treat approach gave $\chi^2=6.68$ for day 15 and $\chi^2=8.24$ for day 29, which both exceed the critical value 6.02.

Table I summarises the recruitment, loss, and

withdrawal of patients. There were five treatment failures, all in the sucralfate group.

The treatment groups were well matched for selected patient characteristics (Table II).

ULCER HEALING

Table III shows the healing rates in the two treatment groups for each of the two cohorts, in addition to the 98.6% (adjusting the 95% limit for the effect of interim analysis according to O'Brien and Flemming) confidence limits for the differences in healing rates between the groups. In both analytical cohorts and on all study days the cumulative healing rates were higher in the omeprazole group than in the sucralfate group. A survival type test was not performed because we did not want to overlook a possible superior effect of sucralfate after a two week treatment period.

ULCER PAIN

Table IV compares the duration of symptoms during the last two days in the two groups. At day 15 omeprazole was more efficient than sucralfate in relief of daytime and nocturnal epigastric pain (standard χ^2 test, $p=0.0002$ and $p=0.04$ respectively), nausea (Mantel-Haenszel test, $p=0.0004$), and heartburn (Mantel-Haenszel test, $p=0.003$).

UNEXPECTED SYMPTOMS AND LABORATORY FINDINGS

Three patients (one in the omeprazole group) were withdrawn because of intercurrent disease (heart attack, vomiting, and inability to take oral medication, raised alkaline phosphatase activity because of a gall stone), none were related to the study treatment. In the omeprazole group three patients reported transient headaches, one dizziness, one diarrhoea, two constipation. In the sucralfate group one patient reported nausea and one influenza.

In several cases a single laboratory value fell outside the reference range, but such abnormalities occurred at random in both treatment groups, and none of these abnormalities could be related to the study treatment.

FOLLOW UP STUDY

A total of 51 patients from the omeprazole group and 44 from the sucralfate group entered the follow up study. Nine patients from the sucralfate group and two from the omeprazole group were excluded from survival analysis because of non-compliance and loss to follow up.

At the end of the follow up period the estimated proportion of patients with ulcer relapse was, according to the survival curve, 64 per cent in the sucralfate group and 42 per cent in the omeprazole group (Fig 1). A log rank test gave $\chi^2=6.64$ ($p=0.01$) and hence rejected the hypothesis of equal treatment effects. Thus, the pattern of remission was more favourable among the omeprazole treated patients than among the patients treated with sucralfate. The proportion of patients with ulcer relapse after 360 days was

TABLE III Healing rates for two analytical cohorts, tabulated by treatment group

Cohort	Cumulative healing rates (wk)	Omeprazole v sucralfate				
		Omeprazole patients (n) (%)	Sucralfate patients (n) (%)	Observed difference (%)	98.6% Confidence limits	p Value
'Per protocol' cohort	2	24/49 (49)	11/48 (23)	26	3 to 49	0.01
	4	39/47 (83)	26/44 (59)	24	1 to 47	0.01
	6	45/50 (90)	30/43 (70)	20	0 to 40	0.02
'Intention to treat' cohort	2	25/52 (48)	12/52 (23)	25	3 to 47	0.01
	4	42/52 (81)	27/52 (52)	29	7 to 51	0.002
	6	46/52 (89)	32/52 (62)	27	7 to 47	0.002

TABLE IV Symptoms in 'per protocol' cohort

Symptoms	Omeprazole				Sucralfate			
	Entry (n)	Week 2	Week 4	Week 6	Entry (n)	Week 2	Week 4	Week 6
Daytime epigastric pain	47	7	3	5	44	23	10	7
Nocturnal epigastric pain	34	5	1	1	35	13	10	3
Regurgitation	18	1	2	2	21	6	3	2
Nausea	23	0	0	0	20	9	6	3
Heartburn	27	2	1	1	24	11	6	5

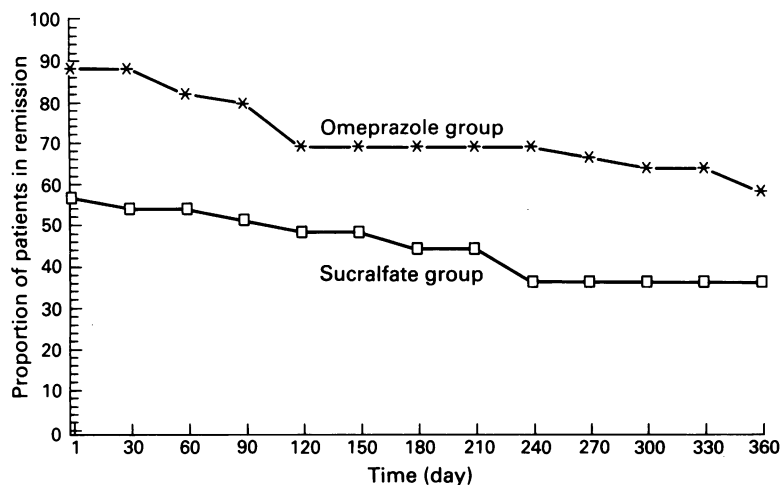


Figure 1: The proportion of patients in remission during 12 months after treatment with omeprazole or sucralfate ($p < 0.01$).

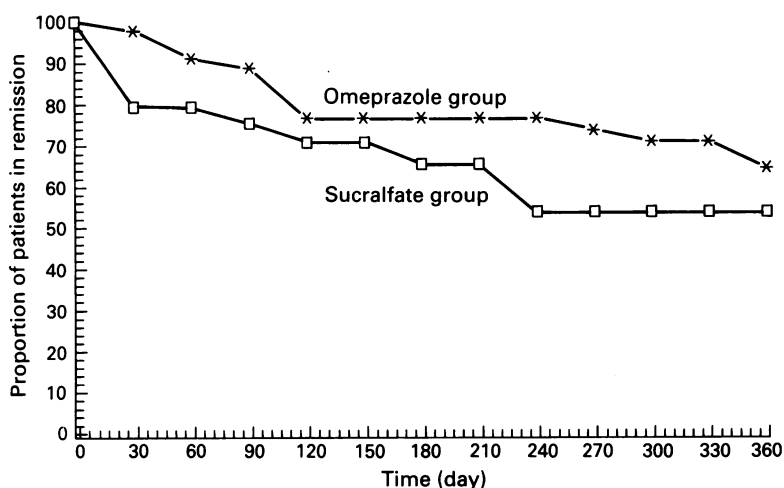


Figure 2: The proportion of patients in remission during 12 months after treatment with omeprazole or sucralfate, considering only those with healed ulcers at end of active treatment ($p = NS$).

46% for sucralfate and 35% for omeprazole considering only those with healed ulcer at the end of active treatment (NS), Figure 2.

Discussion

This is the first study comparing omeprazole in the treatment of peptic ulcer with a non-acid inhibiting agent. We found that omeprazole is superior to sucralfate in accelerating ulcer healing and bringing pain relief. The study was stopped after the first interim analysis.

In accordance with other studies, there was a poor correlation between healing and pain relief.^{1,2,4,10,11} Most patients in both groups were free from pain after two weeks. The results confirm the effect of omeprazole on prepyloric ulcers. The healing rates in the omeprazole group are of the same magnitude as in a previous study⁴ in contrast with sucralfate, which had lower healing rates than cimetidine. This benefit was obtained without serious adverse events. The differences seen in healing rates and fre-

quencies of patients without pain and the 95% confidence limits for the therapeutic gain are possibly of clinical importance. The benefit is less discernible than in patients with duodenal ulcer although it is generally believed that prepyloric ulcers resemble duodenal ulcers with regard to acid secretory pattern.³

In the follow up study only symptomatic patients had an endoscopy. The relapse rate might have been higher if the asymptomatic patients were included. The follow up study showed that more patients were in remission in the omeprazole group than in the sucralfate group after 12 months. This difference was related to the primary healing rates. There was no significant difference in the proportion of patients with ulcer relapse when only those patients with healed ulcers at end of active treatment were considered. Omeprazole healed a greater proportion of patients, however, than sucralfate, and, being more effective, omeprazole also healed the more severe cases and these might have been more prone to relapse. This has, however, not been shown. Thus the group of patients healed by omeprazole is not comparable with the group of patients healed by sucralfate regarding time in remission and relapse time.¹²

In conclusion, omeprazole was shown to heal a higher proportion of patients, provided more pronounced symptom relief, and resulted in more patients in remission during 12 months after treatment was stopped compared with sucralfate in patients with prepyloric ulcer.

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