A double-blind, randomized comparison of omeprazole Multiple Unit Pellet System (MUPS) 20 mg, lansoprazole 30 mg and pantoprazole 40 mg in symptomatic reflux oesophagitis followed by 3 months of omeprazole MUPS maintenance treatment: a Dutch multicentre trial

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Background Proton pump inhibitors (PPIs) have proved to be effective in treating reflux oesophagitis. Until now, no study had compared the PPIs omeprazole Multiple Unit Pellet System (MUPS), lansoprazole and pantoprazole in patients with reflux oesophagitis.

Aim To compare omeprazole MUPS 20 mg, lansoprazole 30 mg and pantoprazole 40 mg for treatment effect in symptomatic reflux oesophagitis.

Method Patients with grade I–IV symptomatic reflux oesophagitis were randomized to double-blind omeprazole 20 mg once morning, lansoprazole 30 mg o.m. or pantoprazole 40 mg o.m. Patient satisfaction and symptoms were evaluated after 4 and 8 weeks. Patients not satisfied after 8 weeks were treated for another 4 weeks with omeprazole 40 mg MUPS (open). Successful treatment was followed by 3 months' maintenance treatment with omeprazole MUPS 20 mg (patients satisfied after 4 or 8 weeks) or omeprazole MUPS 40 mg (patients satisfied after 12 weeks).

Results On intention-to-treat (ITT) analysis (n = 461) at 4 and 8 weeks, respectively, 84% and 87% (omeprazole MUPS), 78% and 81% (lansoprazole), and 84% and 89% (pantoprazole) were free of heartburn. Equivalence was found between omeprazole MUPS and pantoprazole (heartburn relief), but not with lansoprazole. Patient satisfaction after 4 and 8 weeks, respectively, was 79% and 89% (omeprazole MUPS), 76% and 86% (lansoprazole), and 79% and 91% (pantoprazole). Patient satisfaction was similar in all treatment groups. During maintenance, 87% in the omeprazole MUPS 20 mg group and 81% in the omeprazole MUPS 40 mg group were satisfied after 3 months.

Conclusions Omeprazole MUPS 20 mg and pantoprazole 40 mg have equivalent efficacy in the treatment of reflux oesophagitis. Based on patient satisfaction, omeprazole MUPS 20 mg, lansoprazole 30 mg and pantoprazole 40 mg are equally effective. Eur J Gastroenterol Hepatol 14: 649–656 © 2002 Lippincott Williams & Wilkins

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Introduction

Reflux oesophagitis is a common disorder in Western countries [1]. Patients experience considerable impairment in quality of life [2]. Reflux of gastric acid is considered to play a central pathogenetic role. Several studies have shown proton pump inhibitors (PPIs) to be very effective in the treatment of reflux oesophagitis. In addition, many reflux oesophagitis trials have revealed that the PPIs omeprazole 20 mg, lansoprazole 30 mg and pantoprazole 40 mg are equally effective [3–7]. Until now, omeprazole, lansoprazole and pantoprazole have not been compared in one study.

In previous studies, the efficacy of the treatments was evaluated mainly on the basis of endoscopy. However, physicians mostly treat reflux oesophagitis on symptom relief, and endoscopy is performed only in cases of complicated disease or persistent symptoms. Symptom

relief with PPIs has been shown to be a good predictor of healing of oesophageal lesions [8].

In previous studies [3–7,9], omeprazole and lansoprazole were both administered orally as capsules containing enteric-coated granules, and pantoprazole was administered orally as an enteric-coated tablet. Recently, omeprazole became available as a non-enteric-coated tablet that disintegrates rapidly in the stomach into small enteric-coated pellets mimicking the capsule formulation, i.e. a Multiple Unit Pellet System (MUPS) [10,11]. The small pellets can easily pass the pylorus into the small intestine, where they are dissolved. This clearly sets it apart from conventional enteric-coated tablets (e.g. pantoprazole), which remain whole in the stomach and thus do not release the medication until the tablet is emptied from the stomach. No clinical studies comparing omeprazole MUPS with lansoprazole or pantoprazole in reflux oesophagitis patients have been reported.

To imitate daily practice as much as possible, this study focused on symptom relief instead of endoscopic healing. The study aimed to compare the efficacy of omeprazole MUPS 20 mg once morning (OME), lansoprazole 30 mg o.m. (LAN) and pantoprazole 40 mg o.m. (PAN) with regard to heartburn relief, patient satisfaction and quality of life in patients with endoscopically diagnosed symptomatic reflux oesophagitis grade I–IV (according to the modified Savary–Miller classification) [12].

The chronic relapsing nature of gastro-oesophageal reflux disease (GORD) indicates that long-term treatment is often necessary after successful initial treatment [13]. In this study, patients received 3 months' omeprazole MUPS maintenance treatment upon initial successful PPI treatment to evaluate the efficacy and tolerability of OME in the prevention of symptomatic relapse in reflux oesophagitis patients in symptomatic remission. Besides efficacy evaluation during acute and maintenance treatment with regard to patient satisfaction, symptom relief and quality of life, this study aimed to evaluate the role of Helicobacter pylori and constipation since these factors may be of influence in reflux disease.

Patients and methods

Patients

Four hundred and sixty-one patients aged 18–80 years were randomized into this double-blind study conducted in 31 centres in the Netherlands. Local ethical committee approval was obtained in each centre. All patients gave written informed consent. Patients with symptomatic reflux oesophagitis grade I–IV according to the modified Savary–Miller classification, verified by endoscopy within 10 days prior to inclusion, were included (grade I, linear, non-confluent erosions; grade II, longitudinal, confluent, non-circumferential erosions; grade III, longitudinal, confluent, circumferential erosions that bleed easily; grade IVa, one or several ulcerations in the mucosal transition zone, which can be accompanied by stricture or metaplasia; grade IVb, with the presence of a stricture but without indications of erosions or ulcerations).

Exclusion criteria were gastric and/or duodenal ulcers or erosive bulbitis; previous gastro-oesophageal surgery; pregnancy or lactation; concurrent disease or therapy that may complicate the evaluation of the drug (e.g. gastrointestinal disorders that may impair drug absorption; significant cardiovascular, renal or liver disease; endocrine disease; suspected or confirmed malignancy; use of cytotoxic drugs); use of a PPI during the month preceding the endoscopy; contraindication to use of omeprazole, lansoprazole and/or pantoprazole; participation in a clinical study or treatment with any unregistered drug during the previous month; clinically significant abnormalities in pretreatment assessments or laboratory assessments, not related to the primary diagnosis; previous inclusion in the present study; chronic alcoholism, drug abuse or other conditions associated with poor patient compliance; and requirement of an interpreter.

Study design

The study was divided into two phases. In the acute phase, patients were treated for their symptoms of reflux oesophagitis until they were satisfied (treatment duration 4, 8 or 12 weeks, depending on time to patient satisfaction). In the second, maintenance phase, patients satisfied in the acute phase received maintenance therapy for 3 months to prevent symptomatic relapse. Eligible patients were randomized to receive double-blind therapy with omeprazole 20 mg daily (Losec MUPS, AstraZeneca, the Netherlands), or lansoprazole 30 mg daily (Prezal, Laboratorios Almirall SA, Spain), or pantoprazole 40 mg daily (Pantozol, Byk Leo, Germany) for 4 weeks (± 4 days). This treatment was given for another 4 weeks (± 4 days) if the patient was not satisfied. If the patient was still not satisfied after 8 weeks, the patient was treated for another 4 weeks (± 4 days) with omeprazole 40 mg daily (Losec MUPS).

Patients satisfied after 4 or 8 weeks were eligible to enter the maintenance phase, and were treated with OME 20 mg daily for 3 months (90 ± 6 days). Patients satisfied after 12 weeks' acute treatment were eligible to enter the maintenance phase, and were treated with OME 40 mg daily (Losec MUPS) for 3 months (90 ± 6 days). Patients not satisfied after 4, 8 or 12 weeks left the study, and were treated at the discretion of the physician.

Randomization in the acute phase was performed by a computer-generated list in blocks of three with a 1 : 1 : 1 ratio. The study was rendered double blind with the double-dummy technique. Patients were instructed to take two tablets and one capsule (one containing active medication and two being placebo) half an hour before breakfast every day in the acute treatment phase. In the maintenance phase, patients were instructed to take one tablet each morning. Compliance was assessed by counting the returned study medications. Intake $\leqslant 75\%$ or $\geqslant 125\%$ of the total number of scheduled doses of study drug was considered inadequate compliance.

Assessment

At entry, medical and gastrointestinal disease-specific history was obtained, and a physical examination performed. The severity of reflux oesophagitis symptoms (heartburn, regurgitation, dysphagia) was assessed at each visit during the acute and maintenance phases using a standardized question evaluating the symptom severity during the last 7 days. Symptom severity was scored using a four-point graded Likert scale with the scorings 'none' (no heartburn), 'mild' (present but not interfering with normal activities, e.g. work, sleep, meals; causing little or no discomfort), 'moderate' (occasional interference with daily routine or sleep; causing marked discomfort), and 'severe' (disabling; considerable interference with daily activities and/or sleep). At each visit (except at entry) in the acute and maintenance phases, patient satisfaction was assessed by asking the patient, 'Does the study medication give sufficient control of your symptoms?' 'Symptom free' was defined as no heartburn symptoms during the last 7 days in response to the standard question on symptom severity. 'Patient satisfaction' was defined as a positive response to the standard question on patient satisfaction.

During the first week of treatment, the patients completed a daily diary card, preferably at 8 p.m., recording the number of antacid tablets used and the severity of reflux symptoms during the last 24 h. Quality of life was assessed using a disease-specific quality-of-life instrument, the Gastrointestinal Symptom Rating Scale (GSRS) [14]. This questionnaire was developed for the assessment of upper-gastrointestinal disorders; it includes 15 items and uses a seven-point graded Likert scale. The GSRS questionnaire consists of five dimensions: indigestion, diarrhoea, constipation, abdominal pain and reflux [14,15]. At entry and 4 weeks, patients were asked to complete the GSRS questionnaire. Furthermore, at study entry and 4 weeks, patients were asked for their defecation pattern (frequency, consistency, amount of straining during the last 7 days) to assess constipation. Constipation was defined as a defecation frequency of fewer than three stools per week on a three-point graded Likert scale ($<$ 3/week, 3/week, $>$ 3/week). Any adverse event was recorded at each visit. In the maintenance phase, symptom relief and patient satisfaction were assessed.

Statistical methods

Analyses were performed on an intention-to-treat (ITT) basis for all variables. The sample size was based on the primary aim of this study to investigate whether OME 20 mg, LAN 30 mg and PAN 40 mg are equivalent [16]. On the assumption of a minimal clinical relevant difference in symptom relief of 12.5%, and symptom relief fractions of approximately 80% for all three treatments, 118 evaluable patients per treatment arm were needed to be able to show equivalence between each pair of treatments at a 5% significance level (80% power). Allowing for 25% drop-out, a total of 450 patients were planned to be included. The (cumulative) proportion of symptom-free patients and the (cumulative) proportion of satisfied patients after 4, 8 and 12 weeks in the acute phase were compared between the groups by calculating the 90% confidence interval (CI) of the difference between two treatments in fraction of symptom-free or satisfied patients using the t-distribution; a CI lying completely within -12.5 and 12.5 indicated equivalence.

In addition to these primary analyses, some secondary analyses were performed. All had been planned at the start of this study, and none of these involved analyses of equivalence. The fraction of patients with symptom relief and patient satisfaction after 3 months' maintenance treatment was estimated by calculating a 95% CI using exact methods. The change in proportion of patients suffering from constipation at study entry to the proportion at 4 weeks was analysed using the McNemar test and by calculating 95% CIs of the estimated change using the chi-squared distribution. The difference in symptom relief between H. pylori-positive and H. pylori-negative patients was analysed by calculating a 95% CI using the t-distribution.

From the GSRS questionnaire, the sum of the scores for the five predetermined dimensions and the total score were computed for baseline and after 4 weeks' treatment. If more than 40% of the questions were missing, the dimension was considered to be missing. Differences between treatments in GSRS score were analysed using analysis of covariance with factor treatment and GSRS score at baseline as covariant. Least-square estimates resulting from this model were used to calculate the differences between each pair of treatments, with accompanying 95% CIs calculated using the t-distribution. The percentage of symptom-free patients according to the diary card was calculated using the t-distribution. The mean number of antacid tablets used per day was calculated.

Results

Acute phase

Four hundred and sixty-one patients were randomized to OME 20 mg daily (n = 151), or PAN 40 mg daily (n = 154) or LAN 30 mg daily (n = 156). All patients were included in the ITT analyses. The three groups were comparable for demographic details, gastrointestinal disease and symptom score (Table 1). In the OME 20 mg group, seven patients were withdrawn due to adverse events (n = 2), lack of symptom improvement (n = 4), and loss to follow-up (n = 1). From the PAN 40 mg group, five patients were withdrawn due to adverse events (n = 1), lack of symptom improvement (n = 3), and unwillingness to continue (n = 1). Eleven patients were withdrawn from the LAN group due to adverse events (n = 3), lack of symptom improvement (n = 1), unwillingness to continue (n = 3), and loss to follow-up (n = 4).

Symptom relief and patient satisfaction

After 4 weeks, heartburn was reduced effectively in all groups. Symptom relief at 4 weeks was similar in the OME and PAN groups; 84% of the patients reported no heartburn symptoms in the previous 7 days. LAN seemed less effective in heartburn relief compared with the other two groups: 78% were free of heartburn after 4 weeks (difference OME v. LAN, 90% CI −1.44 to 13.24; difference PAN v. LAN, 90% CI −1.07 to 13.49). After 8 weeks, the cumulative percentages of patients free of heartburn were similar for PAN and OME (89% and 87%, respectively; difference PAN v. OME, 90% CI −4.55 to 7.64). In the LAN group, fewer patients were free of heartburn (81%; difference OME v. LAN, 90% CI −0.79 to 12.81; difference PAN v. LAN, 90% CI 0.94 to 14.17) (Table 2).

Patient satisfaction was similar for the three treatments at 4 and 8 weeks. At 4 weeks (ITT analyses), 79% in the OME and PAN groups and 76% in the LAN group were satisfied with the treatment (difference OME v. LAN, 90% CI −4.04 to 11.68; difference PAN v. LAN, 90% CI −4.94 to 10.80; difference PAN v. OME, 90% CI −8.59 to 6.79). At 8 weeks, 89%, 91% and 86% of the patients treated with OME, PAN and LAN, respectively, were satisfied with the treatment (Table 3) (difference OME v. LAN, 90% CI −2.68 to 9.69; difference PAN v. LAN, 90% CI −0.97 to 10.99; difference PAN v. OME, 90% CI −4.12 to 7.13).

Symptom relief (4 and 8 weeks) was similar for each grade of reflux oesophagitis. A small group of patients (n = 32) were not satisfied at 8 weeks and were treated for 4 more weeks with OME 40 mg daily. This additional treatment satisfied 72% (23/32) of these patients (95% CI 56% to 88%). The analyses on H. pylori-positive and H. pylori-negative patients being free of heartburn showed a trend that a smaller proportion of H. pylori-negative patients than H. pylori-positive patients were free of complaints of heartburn (87% v. 81% after 4 weeks; 90% v. 85% after 8 weeks). No further conclusions could be drawn with regard to differences between H. pylori-positive and H. pylori-negative patients, since the study and its sample size calculation were not designed to do this.

Table 1 Patient characteristics (intention to treat) per treatment

	Omeprazole MUPS (n = 151)	Pantoprazole (n = 154)	Lansoprazole (n = 156)
Age* (years)	51.6 (15.0)	51.2 (14.4)	50.8 (14.5)
Gender (% male : female)	58 : 42	61 : 39	58 : 42
Height* (cm)	174.0 (9.2)	174.3 (10.0)	174.2 (9.5)
Weight* (kg)	81.4 (12.4)	81.3 (14.0)	82.3 (13.4)
BMI*	26.9 (3.8)	26.7 (3.9)	27.0 (3.8)
Duration of reflux disease (N, (%))			
< 1 year	47 (31)	47 (31)	44 (28)
1–5 years	63 (42)	59 (38)	68 (44)
> 5 years	41 (27)	48 (31)	44 (28)
Duration of current episode (N, (%))			
< 1 month	12 (8)	12 (8)	14 (9)
1–6 months	82 (54)	90 (58)	74 (47)
> 6 months	57 (38)	52 (34)	68 (44)
Grade of oesophagitis (N, (%))			
I	87 (58)	93 (60)	94 (60)
II	45 (30)	42 (27)	46 (29)
III	11 (7)	16 (10)	10 (6)
IVa	8 (5)	3 (2)	6 (4)
IVb	0 (0)	0 (0)	0 (0)
Severity of heartburn (N, (%))			
None	4 (3)	10 (6)	5 (3)
Mild	38 (25)	32 (21)	32 (21)
Moderate	69 (46)	74 (48)	64 (41)
Severe	40 (26)	38 (25)	55 (35)
Helicobacter pylori (% positive : negative)	22 : 78	24 : 76	28 : 72
Defecation frequency (N, (%))			
< 3/week	11 (7)	9 (6)	5 (3)
3/week	9 (6)	10 (6)	7 (5)
> 3/week	131 (87)	135 (88)	142 (92)
GSRS score*	2.9 (0.8)	2.9 (0.9)	2.8 (0.9)

BMI, body mass index; GSRS, Gastrointestinal Symptom Rating Scale; MUPS, Multiple Unit Pellet System.
*Mean (standard deviation).

Table 2 Proportion of patients with complete heartburn relief after 4 and 8 weeks

Weeks	OME 20 (%)	LAN30 (%)	PAN40 (%)
4	84*	78	84*
8	87*	81	89*

LAN, lansoprazole 30 mg o.m.; OME, omeprazole Multiple Unit Pellet System (MUPS) 20 mg o.m.; PAN, pantoprazole 40 mg o.m.
*Omeprazole (MUPS) and pantoprazole equally effective after 4 and 8 weeks.

Table 3 Proportion of patients satisfied after 4 and 8 weeks

Weeks	OME 20 (%)	LAN30 (%)	PAN40 (%)
4	79	76	79
8	89	86	91

LAN, lansoprazole 30 mg o.m.; OME, omeprazole Multiple Unit Pellet System (MUPS) 20 mg o.m.; PAN, pantoprazole 40 mg o.m.
All three treatments equally effective after 4 and 8 weeks.

Constipation assessment

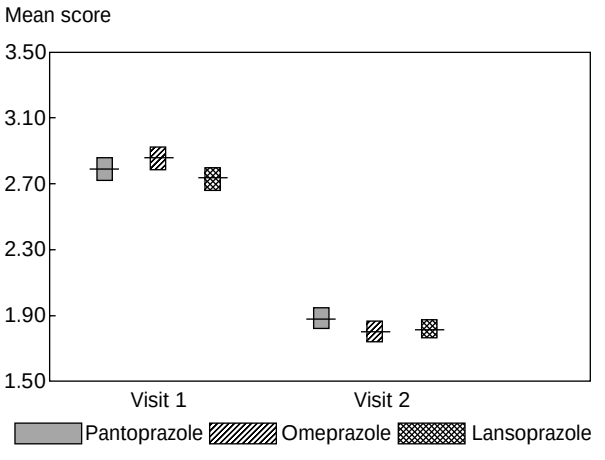
The observed proportion of patients suffering from constipation at baseline was only 5%. At 4 weeks, this proportion declined to 2.7% (95% CI 0.3% to 5.1%, $P < 0.05$).

Gastrointestinal Symptom Rating Scale and diary card assessments

At baseline, a total GSRS score of 2.86 (95% CI 2.81 to 3.00) was observed. The highest symptom score was found for the dimensions reflux syndrome (mean score 3.83, 95% CI 3.61 to 4.05), indigestion syndrome (mean score 3.48, 95% CI 3.27 to 3.70), and abdominal pain (mean score 3.18, 95% CI 2.97 to 3.38). Baseline scores for other dimensions were lower (constipation mean score 2.00, 95% CI 1.82 to 2.20; diarrhoea mean score 1.92, 95% CI 1.73 to 2.11).

For all treatments, patients scored significantly fewer symptoms in the GSRS questionnaire after 4 weeks compared with baseline (Fig. 1). Especially on reflux syndrome, indigestion and abdominal pain, a considerable improvement was observed: reflux decreased to 1.54 (95% CI 1.38 to 1.69; difference −2.29), indigestion decreased to 2.32 (95% CI 2.13 to 2.52; difference −1.16), and abdominal pain decreased to 1.99 (95% CI 1.81 to 2.16; difference −1.19). Lower GSRS scores mean less gastrointestinal discomfort perceived. In general, a change of 0.5 on a seven-point Likert scale is considered to be clinically relevant. When comparing the three treatments for mean total GSRS score corrected for baseline, no differences were found. For the separate dimensions, except for abdominal pain, no significant difference was found in GSRS score corrected for baseline. A significant difference was found between OME 20 mg and PAN 40 mg. Patients treated with PAN suffered more symptoms of abdominal pain after 4 weeks' treatment than OME-treated patients. The diary cards suggested no differences in symptom relief. The mean number of antacid tablets used according to the diary cards was less than one per day and the median intake was equal to zero on all days for all treatments.

Fig. 1



Total score Gastrointestinal Symptom Rating Scale (GSRS). Mean scores (with 95% confidence intervals) in gastrointestinal symptoms at baseline (visit 1) and after 4 weeks (visit 2).

Withdrawals and adverse events

In total, 73 (16%) patients reported one or more adverse events. In all three groups, adverse events reported were comparable in number, type, causality rating and severity. The most common adverse events were diarrhoea (OME, $n = 5$; PAN, $n = 4$; LAN, $n = 6$), headache (OME, $n = 3$; PAN, $n = 3$; LAN, $n = 5$) and nausea (OME, $n = 3$; PAN, $n = 1$; LAN, $n = 6$). In six cases (OME, $n = 2$; PAN, $n = 1$; LAN, $n = 3$), adverse events caused withdrawal from the study. Four patients were hospitalized (one chronic obstructive pulmonary disease (COPD) exacerbation; one allergic reaction to soya; one venous thrombosis and pulmonary embolism; one ruptured cerebral aneurysm). None of these serious adverse events was considered to be related to the treatment.

Maintenance phase

Three hundred and ninety-one patients satisfied in the acute phase were included in the maintenance phase. Most of these ($n = 370$) were satisfied after 4 or 8 weeks' acute treatment and were therefore allocated to treatment with OME 20 mg daily in the maintenance phase. A small proportion of patients ($n = 21$) were not satisfied until 12 weeks. These patients were allocated to OME 40 mg daily for 3 months. At entry of the maintenance phase, 93% of the satisfied patients entering the OME 20 mg maintenance group, and 81% of the satisfied patients entering the OME 40 mg maintenance group, had no heartburn complaints. Twenty-two patients discontinued the study prematurely due to adverse events ($n = 9$), lack of efficacy ($n = 6$), unwillingness to continue ($n = 4$), and loss to follow-up ($n = 3$).

Symptom relief and patient satisfaction

After 3 months of treatment, 87% of the patients treated with OME 20 mg were satisfied, and 81% of the patients treated with OME 40 mg were satisfied. Most patients were still free of heartburn complaints (OME 20 mg, 85%; OME 40 mg, 81%). Symptom relief with OME 20 mg was independent of initial treatment or initial severity of reflux oesophagitis. The number of patients in the OME 40 mg group ($n = 21$) was too small to be divided further into initial treatment or initial reflux oesophagitis grading.

Withdrawals and adverse events

Adverse events were recorded for 73 (19%) patients. Adverse events were comparable to those reported in the acute treatment phase. The most common adverse events were abdominal pain (n = 10), diarrhoea (n = 6), dizziness (n = 6), nausea (n = 6) and dyspepsia (n = 2). In nine cases, adverse events caused withdrawal from the study. Five patients were hospitalized (one tuberculosis [the same patient that was hospitalized in the acute treatment phase due to COPD exacerbation], one epistaxis, one suicide attempt, one to have cerumen removed from the membrana tympani, one diabetes insipidus). None of these serious adverse events was considered to be related to the study medication.

Discussion

Previous studies have showed omeprazole 20 mg, lansoprazole 30 mg and pantoprazole 40 mg to be similarly effective in treating reflux oesophagitis and its symptoms [3–7]. This study confirms that PPIs are highly effective in the treatment of symptoms of reflux oesophagitis: 82% and 86% of the patients (average of the three treatments) were free of heartburn after 4 and 8 weeks' treatment, respectively. These findings are supported by the results on patient satisfaction: 78% after 4 weeks and 89% after 8 weeks.

Additional benefit of OME 40 mg was found in 72% of the patients not satisfied after 8 weeks' treatment with OME 20 mg, LAN 30 mg or PAN 40 mg. This additional benefit resulted in a total proportion of 94% satisfied patients, when adding to the patients who were satisfied after 4 or 8 weeks of treatment. These results confirm the additional benefit of omeprazole 40 mg over omeprazole 20 mg as observed previously by Bate et al. [17] in patients who do not respond adequately to treatment with a standard daily dose of omeprazole 20 mg. It must be noted, however, that the additional 4 weeks' treatment (independent of dose) and a placebo effect (open treatment) may have contributed to the additional benefit of 4 weeks' OME 40 mg treatment.

Symptom relief was not correlated to the severity of oesophagitis at entry. In some previously performed trials on healing of reflux oesophagitis during PPI treatment [9,18], no relationship between endoscopic grade at entry and healing after 4 weeks' PPI treatment could be established, while other authors suggested a relationship between the baseline grade of oesophagitis on the overall healing [3,5–7,19]. Since correlation between symptoms and endoscopic severity seems to be poor [1,20,21], it is not surprising that in this study no correlation was found between symptom relief and oesophagitis severity at entry. It should be realized that the number of patients with severe reflux oesophagitis (grades III and IV) in this study was quite low (n = 54; 12%).

It has been suggested that constipation could be a partial cause of the reflux symptoms [22]. In this study, however, only 5% of the patients suffered from constipation at entry. Therefore, constipation does not seem to be a relevant factor in reflux oesophagitis. This is also supported by the GSRS results (mean constipation score 2.00 v. 1.55 in normal population) [14].

Currently, the influence of H. pylori infection on GORD is a major focus of attention [23,24]. It has been suggested that H. pylori-positive patients have milder reflux symptoms than H. pylori-negative patients due to the pH-increasing effect of H. pylori [25–27]. In addition, H. pylori affects the management of reflux disease since H. pylori may increase the efficacy of acid-suppressive therapy [28], and development of reflux oesophagitis after H. pylori eradication in duodenal ulcer patients has been reported [29]. An evaluation of pooled data from 858 patients with reflux oesophagitis found no effect of H. pylori status on reflux oesophagitis healing and heartburn control [30]. Others have showed that PAN 40 mg once daily was significantly more likely to produce healing of oesophagitis in H. pylori-positive patients at 4 and 8 weeks when compared with H. pylori-negative patients [31]. In our study, no differences in reflux disease or other demographics existed between H. pylori-positive and H. pylori-negative patients at baseline. A trend was observed for a bigger proportion of H. pylori-positive patients being symptom free compared with H. pylori-negative patients (87% v. 81% after 4 weeks; 90% v. 85% after 8 weeks). The hypothesis of a beneficial effect of H. pylori infection on the treatment outcome in patients with reflux disease seems to be supported by our observations, but this should be tested further.

Other than assessing the therapeutic effect on symptoms, the present study also evaluated the patients' quality of life using the disease-specific GSRS questionnaire. At entry, patients showed a moderately impaired quality of life, caused mainly by reflux symptoms, indigestion and abdominal pain. The contribution of reflux, indigestion and abdominal pain to impaired quality of life was also observed in previous trials using the GSRS questionnaire [14,15,32]. The improvement in overall quality of life score at 4 weeks confirms the observed symptom improvement and high patient satisfaction scores after 4 weeks' PPI treatment. As is to be expected in patients suffering from reflux oesophagitis, the most severe symptom score and most pronounced improvement of quality of life was obtained in the dimension reflux symptoms: a decrease from 3.83 at baseline to 1.53 after 4 weeks of treatment,

thus approaching the normal score on reflux symptoms of 1.39 [14].

With respect to adverse events suspected to be related to the study therapy, the three treatments showed few and mostly mild adverse events. Side effects were comparable in all three PPIs.

With regard to the prevention of symptomatic relapse, this study confirms the efficacy of omeprazole to keep patients in symptomatic remission, independent of the initial treatment or initial endoscopic severity of reflux oesophagitis [14,33–37]. The new MUPS formulation proved its efficacy and good tolerability in the treatment of symptomatic reflux oesophagitis patients.

In conclusion, this trial confirms that OME 20 mg, LAN 30 mg and PAN 40 mg are highly effective in the treatment of symptoms of reflux oesophagitis, providing adequate symptom control and improved quality of life. OME 20 mg and PAN 40 mg showed similar efficacy in the symptomatic treatment of reflux oesophagitis. LAN 30 mg was shown to be not as effective in heartburn relief as OME 20 mg and PAN 40 mg, but this was not supported by the other variables studied. The fact that no equivalence was found for heartburn relief for LAN compared with OME and PAN does not imply that a difference exists between the treatments; the study was designed not to show differences but to test for equivalence, and therefore no conclusions can be drawn with regard to differences between treatments.

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