Maintenance therapy with pantoprazole 20 mg prevents relapse of reflux oesophagitis

J. ESCOURROU*, P. DEPREZ†, A. SAGGIORO‡, H. GELDOF§, R. FISCHER¶, C. MAIER¶ & THE EUROPEAN PANTOPRAZOLE STUDY GROUP

*CHU Toulouse Rangueil, Toulouse, France; †UCL Cliniques St Luc, Brussels, Belgium; ‡Ospedale Umberto I, Mestre, Italy; §Ijsselland Ziekenhuis, Capelle A/D Ijssel, the Netherlands; and ¶Byk Gulden, Konstanz, Germany

Accepted for publication 26 July 1999

SUMMARY

Background: Proton pump inhibitors can be effective as maintenance therapy in reducing the relapse rate of reflux oesophagitis at a dose lower than that used for acute healing.

Patients and methods: Patients (n = 396, 18–88 years old) with healed reflux oesophagitis (grade II or III before healing) were included in this multinational, prospective, parallel-group, randomized double-blind study. They took oral pantoprazole 20 mg (n = 203) or 40 mg (n = 193), once daily for up to 12 months. Scheduled endoscopies were performed at entry, after 6 and 12 months, or when symptoms of at least moderate intensity were perceived on 3 consecutive days; symptoms were assessed every 3 months. The primary efficacy parameter was the time until endoscopically proven relapse of reflux oesophagitis occurred; the

secondary parameters included tolerability, safety and time until symptomatic relapse occurred.

Results: Analysis was performed using the 'all-patientstreated' approach. Endoscopic relapse rates in the 20 mg group after 6 and 12 months were 16 and 29%, respectively; in the 40 mg group, they were 7 and 19%, respectively. Symptomatic relapse rates after 6 and 12 months were 14 and 21% in the 20 mg group and 10 and 17% in the 40 mg group, respectively. Pantoprazole 20 mg and 40 mg were well tolerated throughout the study; the type and frequency of adverse events reported were similar for both treatment groups. Conclusion: The 20 mg dose was proven to be 'at least equivalent' to the 40 mg dose with respect to endoscopic and symptomatic relapse. The 20 mg once daily dose represents an effective and safe maintenance regimen for the majority of patients with healed reflux oesophagitis.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) affects up to 40% of adults in Great Britain and the USA.^{1, 2} GERD is multifactorial in aetiology and has several pathophysiological mechanisms that may be responsible for its development.³ Treatment of GERD involves therapies with drugs that have either prokinetic or antisecretory

Correspondence to: Prof. J. Escourrou, Hôpital de Rangueil, 1, avenue Jean Poulhes, F-31403 Toulouse Cedex 4, France. E-mail: escourrou.j@chu-toulouse.fr properties. The former approach converges on the primary motility disorder that leads to reflux.⁴ The latter, which is currently the option recommended for patients with more severe grades of GERD, is based on elevating gastric pH and decreasing the volume of gastric juice (hence of the refluxate).⁵

Gastric pH can be controlled to some extent with histamine-2 receptor antagonists (H₂-RAs) and these drugs have been the mainstay of antisecretory therapy in the past. However, with the advent of proton pump inhibitors, the efficacy of H₂-RAs has been overshadowed, particularly in the treatment of patients with GERD. Over 90% of patients with endoscopically diagnosed moderate to severe GERD (grade II or III, Savary–Miller classification⁶) can be healed during short-term treatment with a proton pump inhibitor; this compares to about 45% of patients healed following treatment with H₂-RAs.^{7–13} The higher rate of oesophageal healing is probably due to the proton pump inhibitors' successful ability to elevate intragastric pH to higher levels and for a longer duration than the H₂-RAs. Moreover, proton pump inhibitors are not subject to the development of tolerance—a well-known disadvantage of H₂-RAs.^{11, 14, 15}

Acute reflux oesophagitis can clearly be healed by short-term regimens with antisecretory drugs. However, unless maintenance treatment is provided, patients tend to relapse with reflux oesophagitis at a rate of more than 80% in the first 6–12 months.^{12, 16, 17} Apart from the discomfort caused by the relapses, reflux oesophagitis could initiate morphological changes in the oesophagus resulting in complications that may include the development of oesophageal strictures, columnar cell replacement, or both.¹⁸ Therefore, for patients with recurrent reflux oesophagitis, long-term antisecretory therapy with proton pump inhibitors is recommended in order to minimize symptomatic and endoscopic relapses.^{4, 5, 17, 19–21}

Recent studies indicate that patients with healed reflux oesophagitis can remain in remission even with a dose of proton pump inhibitor that is lower than that used for healing of the acute reflux oesophagitis.^{12, 20, 22, 23} This approach was tested in the present study, using oral doses of 20 mg and 40 mg pantoprazole, administered as maintenance therapy for up to 12 months. Pantoprazole is a potent and safe proton pump inhibitor, which has been used clinically for the treatment of reflux oesophagitis and other gastric acid-related diseases.^{10, 24}

PATIENTS AND METHODS

Study design

This was a prospective, randomized, double-blind study, involving 52 centres in Belgium, France, Italy and the Netherlands. It was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice. It was approved by the respective Ethics Committees and all patients gave their written informed consent prior to their participation in the study.

Inclusion criteria

Prior to the long-term maintenance study, patients with endoscopically diagnosed GERD grade II or III were enrolled into a short-term study to heal the acute reflux oesophagitis. Included in the short-term study were male and female patients (n = 460)presenting with reflux oesophagitis grade II (82%) or III (18%), according to the Savary-Miller classification.⁶ The short-term study lasted for 4 weeks and, if the healing was not complete (as assessed by endoscopy), the treatment continued for another 4 weeks. During the healing phase, patients received either pantoprazole 40 mg or omeprazole 20 mg (double-blind, parallel-group, multinational, multicentre study design); complete, endoscopically-confirmed healing rates were 95 and 96%, respectively (per protocol). Irrespective of the treatment during the short-term study, patients with an initial GERD grade II tended to heal faster than those with GERD grade III.

For the long-term maintenance study a total of 396 patients with completely healed oesophagitis (age range 18–88 years) were enrolled. Their demographic and anthropometric data are summarized in Table 1.

Table 1. Demographic and anthropometric data for the patient population enrolled into the long-term maintenance therapy study

	Pantoprazole			
Parameter	20 mg	40 mg		
Number of patients	203	193		
Gender distribution	56F/147M	53F/140M		
Median age (years)	50	50		
Range	20-84	18-88		
Median height (cm)	172	170		
Range	145-192	150-202		
Median weight (kg)	76	75		
Range	42-130	48-125		
Median body mass index (kg/m ²)	25.7	25.6		
Range	19.2 - 47.5	16.8 - 39.5		
Smokers (%)	40 (20%)	35 (18%)		
GERD at diagnosis				
Grade II	162 (80%)	159 (82%)		
Grade III	41 (20%)	34 (18%)		

The long-term maintenance therapy consisted of pantoprazole 20 mg or 40 mg, administered once daily for up to 12 months. GERD at diagnosis refers to the grade of reflux oesophagitis diagnosed initially at the start of the short-term healing study.

© 1999 Blackwell Science Ltd, Aliment Pharmacol Ther 13, 1481-1491

Exclusion criteria

Exclusion criteria were the presence of a peptic ulcer and ulcer complications, intake of supportive medication for the management of GERD during the study, regular and continued intake of glucocorticoids, ulcerogenic medications such as non-steroidal antiinflammatory agents, or simultaneous intake of drugs whose absorption is pH-dependent, such as ketoconazole. Pregnant and nursing women, women of child-bearing age without reliable contraception, clinically relevant deviations from the normal range in laboratory parameters as assessed by the investigator, and patients who could not be expected to comply with the treatment were also excluded.

Treatment

Patients were allocated to one of two treatment groups according to a computer-generated randomization list; they took either 20 mg (n = 203) or 40 mg (n = 193) pantoprazole tablets, once daily before breakfast, for up to 12 months. The double-blind design of the study was ensured by using tablets that were identical in appearance.

Assessments

Follow-up visits were performed at 3, 6, 9 and 12 months after the first intake of the study medication. Scheduled endoscopies were performed at entry, and after 6 and 12 months. Patients who perceived symptoms of reflux oesophagitis of at least moderate intensity for at least 3 consecutive days between the scheduled study visits were asked to contact the investigator and an additional endoscopy was performed. Patients with endoscopically-verified relapse of oesophagitis, grade I–IV (Savary–Miller classification⁶) or a peptic ulcer were excluded from further participation in the study; they were treated at the discretion of the attending physician.

The presence and severity of the principal symptoms of reflux oesophagitis included acid regurgitation, heartburn and pain on swallowing, and were defined as follows: *heartburn*, substernal pain or burning sensation in the epigastrium, possibly rising to the pharynx; *acid regurgitation*, backward flow of small amounts of the stomach contents, possibly rising to the pharynx and attributed to gastric acid which could sometimes occur

© 1999 Blackwell Science Ltd, Aliment Pharmacol Ther 13, 1481-1491

together with coughing or choking; *pain on swallowing*, associated with retrosternal tightness.^{25, 26} Patients were asked at each visit to classify the severity of their symptoms as *mild*, barely noticeable, *moderate*, clearly noticeable symptoms, but tolerable without immediate relief, or *severe*, overwhelming discomfort, urgent desire for immediate relief.

The grading of endoscopically-proven reflux oesophagitis was defined according to Savary & Miller⁶ as follows: *Grade I*, presence of erythematous, oval or linear erosions above the mucosal transition; further multiple lesions may appear with time, however they must not become confluent; *Grade II*, lesions described for Grade I become confluent but do not cover the whole circumference; they are often covered by a fibrous layer; *Grade III*, exudative erosions can cover the whole circumference of the oesophagus; *Grade IV*, involves the complications associated with ulcer, stenosis, brachyoesophagus and columnar cell replacement.

Efficacy parameters

The primary efficacy parameter was defined as the time (up to 12 months) until the patient had an endoscopically-proven relapse. The secondary criterion of efficacy was the symptomatic relapse of reflux oesophagitis, defined as the time (up to 12 months) until a symptomatic relapse of leading or other gastrointestinal symptoms of GERD of at least moderate intensity occurred.

Supportive medication

With the exception of a defined amount of antacids, the intake of other supportive medications for the treatment of GERD was not permitted during the study. When a patient perceived symptoms of GERD for at least 3 consecutive days and when an endoscopic relapse of GERD was excluded, antacids could be ingested over a maximum of 7 days. Ingestion of antacids without prior endoscopy was disallowed. If symptoms persisted despite the intake of antacids for 7 days, the patient was withdrawn from the study and rated as a symptomatic relapse.

Compliance

Compliance with the study medication was required to be greater than 70% between two study visits; this was checked by counting the returned tablets. Attendance at the follow-up visits had to occur within 7 days of the scheduled date. However, about one-third of the patients attended the study visit more than 10 days outside the scheduled date (earliest -28 days and latest +28 days). This was considered to be not clinically relevant and was dealt with as an accepted deviation from the protocol.

Safety

The safety of the study medication was assessed by monitoring adverse events, and analysis of biochemical and haematological laboratory parameters (listed below). Patients were asked to report any adverse events to the investigator. The causal relationship between the adverse event and the study medication was made by the investigator and assessed as 'not related', 'possibly related' or 'definitely related'.

Haematological and biochemical parameters were determined at all study visits. Patients were fasted when specimens for the following parameters were obtained: *blood*, haemoglobin, erythrocytes, leucocytes, thrombocytes; *serum*, glucose, creatinine, total bilirubin, concentration of liver enzymes in serum (glutamic-oxaloacetic transaminase, serum glutamate pyruvate transaminase), alkaline phosphatase, total cholesterol, triglycerides, gastrin; *urine*, protein, glucose, blood cells. Except for gastrin, which was determined centrally in each country, all other parameters were analysed by the laboratories of the respective study centres.

Statistics

Determination of sample size. For the long-term study, about 150 patients per treatment group were expected to be enrolled. This calculation was based on the assumption that a 90% healing rate would be achieved during the short-term healing study, and that at least 80% of the healed patients would participate in the long-term study. Having 150 patients per treatment group and 90% as the average rate of patients in remission after 12 months would allow detection of a 10% difference at the $\alpha = 5\%$ level of significance with a power of more than 80% (Fisher's exact test used as an approximation to the Kaplan–Meier, to estimate the difference in relapse rates, 85%:95%, $\beta = 13\%$).

Patient populations and discontinuations. It is known that endoscopically-confirmed relapse of reflux oesophagitis is not always accompanied by symptoms and vice versa. To accommodate such possibilities in the present study, stringent conditions were applied for the statistical evaluation of the therapeutic efficacy of pantoprazole. Estimation of the rates of endoscopic remission after 6 and 12 months, and symptomatic remission after 3, 6, 9 and 12 months, were calculated according to the Kaplan–Meier life-table analysis, with 95% confidence limits. For the comparison between the treatment groups, the difference and its 90% confidence limits were calculated for each time point; the time until healing was compared by means of the log-rank test.

The definitions used for the analyses of endoscopic and symptomatic relapse rates, drop-outs and protocol violators are summarized in Table 2. Protocol violators were patients who showed major breaches of the study protocol; they were evaluated identically as 'censored' patients from the respective time point (Table 2).

Endoscopic relapse. Remission rates and the corresponding standard errors for each treatment and time point were estimated using the life-table analysis according to Kaplan–Meier. Therapeutic 'at least equivalence' was concluded if the lower limit of this interval was above -20%. Additionally, the log-rank test was used to compare the time until relapse occurred (defined as '6 months' and '12 months' and representing the observation periods of 0–6 months and 6–12 months, respectively).

This analysis was performed using the 'all patients treated' approach which included all patients who provided at least one set of evaluable follow-up information. Patients terminating the study due to an adverse event that was considered to be 'possibly' or 'definitely' related to the study medication or due to lack of efficacy, presenting for example as intolerable symptoms, were evaluated as 'endoscopic relapse' from the respective time point (Table 2).

Symptomatic relapse

Symptomatic relapses were evaluated using the same methods as described above for the endoscopic relapses, but using the 'per protocol' approach; patients also included in this analysis were those

^{© 1999} Blackwell Science Ltd, Aliment Pharmacol Ther 13, 1481-1491

Endoscopic relapse	Censored	Symptomatic relapse	Censored
Endoscopy: endoscopically verified reflux oesophagitis (grade I or greater), or peptic ulcer <i>leading to termination of</i>		Symptoms: presence of at least one key symptom of reflux oesophagitis, perceived in at least moderate intensity and occurring for at	endoscopically verified reflux oesophagitis without symptoms moderate in intensity
the study adverse event possibly or definitely related to study medication (drop-outs)	due to adverse events <i>not</i> <i>related</i> to study medication	least 3 days prior to study visit	premature study termination due to adverse events, <i>independent</i> of the causality assessment
lack of efficacy, i.e. intolerable symptoms leading to premature study termination (<i>drop-outs</i>)	poor compliance – missed study visits, incomplete intake of study medication, concomitant intake of disallowed medications (protocol violators)		poor compliance – missed study visits, incomplete intake of study medications, concomitant intake of disallowed medications

Table 2. Summary of terms and definitions used for the statistical evaluation of therapeutic efficacy during maintenance therapy with pantoprazole 20 mg or 40 mg administered to patients with healed reflux oesophagitis

The 'censored' patients represent those who discontinued the study prematurely but who provided statistically evaluable information up to a time indicated in Tables 3A and 3B.

terminating the study for reasons not related to symptoms, who were evaluated only until the date of the last valid symptom status. The time points included in the analyses were 0, 3, 6, 9 and 12 months, because these were the scheduled times for the assessment of symptoms.

Clinical laboratory parameters and adverse events. All patients who took the study medication at least once were included in the evaluation of safety parameters. These included adverse events and laboratory parameters, which were evaluated descriptively. Baseline comparisons for the variables smoking and alcohol consumption were compared between the treatment groups using the Cochran–Mantel/Haenszel method. The confidence intervals of the group medians were determined for the variables age, body mass index, and the number of preceding relapses.

RESULTS

Patient population

At the time of enrolment into the maintenance study there were no significant differences between the patients randomized for treatment with pantoprazole 20 mg (n = 203) and pantoprazole 40 mg (n = 193) with respect to the demographic and clinical parameters (Table 1). A flow chart, shown in Figure 1, summarizes the disposition of the patients.

Endoscopic relapse

In the 20 mg treatment group, 49 patients were classified as endoscopic relapse. Of these, 45 had endoscopically-confirmed relapse of reflux oesophagitis (grade I n = 35, grade II n = 7, grade III n = 2, and grade IV n = 1). An account of the patients with relapse, including the grade of GERD observed at diagnosis and upon relapse during the long-term treatment, is shown in Figure 2. In addition, endoscopic relapse status was assigned to another four patients because of either adverse events that were rated as 'possibly' or 'definitely' related to the study medication or intolerable symptoms (increased concentration of liver enzymes, taste perversion, insomnia) (Figure 1).

In the 40 mg treatment group, a total of 30 patients were classified as endoscopic relapse. Of these, 29 had endoscopically-verified relapse of reflux oesophagitis (grade I n = 21, grade II n = 8) (Figure 2); one other patient was also classified as an endoscopic relapse due to an adverse event (diarrhoea) that was rated as 'definitely' related to the study medication (Figure 1).

The number of patients with endoscopic relapse at 6 and 12 months, those in remission and completing the study interval, and the probability of endoscopic relapse



Figure 1. Disposition of patients with healed reflux oesophagitis who took part in the maintenance therapy with either 20 mg or 40 mg pantoprazole for up to 12 months. Definitions of protocol violators and drop-outs are summarized in Table 2. The numbers shown here for protocol violators, those with a relapse status, and those completing the study represent the endoscopic relapse (Table 3A). Information regarding the symptomatic relapse can be obtained from Table 3B.

together with its 95% confidence intervals, are summarized in Table 3. The estimated endoscopic relapse rates were 16 and 29% for the 20 mg group at 6 and 12 months, respectively. In the 40 mg group the estimated endoscopic relapse rates were 7% after 6 months and 19% after 12 months.

The 20 mg and 40 mg doses of pantoprazole were judged as therapeutically 'at least equivalent' in preventing endoscopic relapse of reflux oesophagitis at 6 and 12 months because the lower confidence limit of the 90% confidence interval for the difference was above the predefined -20% (Table 4). Hence by inference, an inferiority of more than 20% of one treatment over the other could be statistically excluded. These results are illustrated in Figure 3.

The time to relapse was compared between the two treatment groups by means of the log-rank test. It was shown that pantoprazole 40 mg was superior to 20 mg in preventing endoscopic relapse (P = 0.0368). Thus, there was a statistically significant difference between the two doses, but according to predefined criteria this difference was considered to be not clinically relevant.

Symptomatic relapse

The actual numbers of patients with symptomatic relapse after 3, 6, 9 and 12 months, the probability of

symptomatic relapse and the number of patients completing the corresponding interval are listed in Table 3B. Time to symptomatic relapse, calculated according to the log-rank test, was not significantly different between the two treatment groups (P = 0.9955). Using the same analytical approach as for the endoscopic relapse, a therapeutic 'at least equivalence' of the 20 mg compared to the 40 mg dose of pantoprazole was concluded for the symptomatic relapse rates of reflux oesophagitis (Table 4, Figure 4).

Safety

Adverse events. As summarized in Table 5, a total of 135 adverse events was reported by 97 patients; 53/203 (26%) and 44/193 (23%) of patients were in the 20 mg and the 40 mg treatment group, respectively. The frequency and causality assessment, as well as the type of the most commonly reported adverse events, were similar in both treatment groups. They included elevated serum concentration of liver enzymes, diarrhoea, abdominal pain and bronchitis; they affected between 1 and 3% of the patients participating in the study (Table 5).

Among the adverse events, 14 were rated as serious. Although none of these adverse events were related to the study medication, the events were classified as serious because they involved hospitalization. A total of three patients discontinued the study for the following



PANTOPRAZOLE PREVENTS RELAPSE OF GERD

Laboratory parameters

Results of biochemical and haematological parameters were analysed at each study visit and compared to baseline values. Irrespective of the treatment group, these parameters showed minimal changes in most patients, who all continued with the treatment. For one patient in the 20 mg pantoprazole group, an increase in the serum concentration of liver enzymes was found at the 3 month study visit. It was an adverse event rated as possibly related to the study medication and this patient discontinued the study.

1487

Gastrin

DISCUSSION

During the 12 month treatment period the median concentrations of serum gastrin increased slightly and to a similar extent in both treatment groups. There were no statistical differences in the gastrin values between the treatment groups either at baseline or after 12 months of treatment. In the 20 mg pantoprazole group, the values of the median gastrin values were: 10–56 ng/L at baseline and 22–129 ng/L after 12 months of treatment; in the 40 mg pantoprazole group, the corresponding values were 15–58 ng/L and 10–100 ng/L, respectively.

Figure 2. Account of patients diagnosed with an *endoscopically-verified* relapse. The grade of oesophagitis upon relapse and at the initial diagnosis are indicated. The reason for indicating slightly different numbers in Figures 1 and 2 for patients with a relapse is explained in the Results section. One patient in the 20 mg pant-oprazole treatment group relapsed from an initial GERD grade II at initial diagnosis to grade IV, 3 months after receiving the maintenance treatment. For this patient, poor compliance with the study medication cannot be ruled out as a possible reason for the relapse.

reasons: cardiac draft surgery (n = 1, discontinued the study after 10 months), myocardial infarction (n = 1, discontinued after 4 months), and adenocarcinoma on the right kidney (n = 1, discontinued after 3 months); the other 11 patients who had accidental injury, ileus, cholelithiasis, diarrhoea, psychosis, myocardial ischaemia, neoplasm, colitis, bronchitis and sepsis, continued with the treatment.

Four patients discontinued the study due to adverse events assessed by the investigators as 'possibly' or 'definitely' related to the treatment medication. The adverse events included hyperlipaemia, elevated concentration of liver enzymes in the serum, coughing and taste perversion, insomnia, and substernal chest pain. Preventing a relapse of reflux oesophagitis in successfully healed patients is one of the common challenges facing the attending physician. Studies with H₂-RAs, administered as maintenance therapy, have revealed that between 67 and 87% of patients relapse within the first 6–12 months. This represents a rate similar to placebo or no treatment.^{4, 12, 27} In contrast, controlled studies with proton pump inhibitors (omeprazole, lansoprazole), administered as maintenance therapy, have illustrated that within the first year of treatment the relapse rate can be reduced to between 15 and 45%.²⁰

Maintenance therapies with either omeprazole^{4, 16, 28–31} or lansoprazole^{17, 21, 32} prevent endoscopic relapse in a dose-dependent manner. For both of these drugs, the standard dose, as well as the low dose, are registered for maintenance therapy in patients with healed oesophagitis. Results of controlled studies in such patients have shown that after 12 months of regular maintenance therapy, the relapse rates were 38–50% following

Treatment and period	Number of patien at risk during the study interval (<i>N</i>)	nts Drop-outs and protocol violators (N)	Patients in remission completing the interval (N)	Patients with endoscopic relapse (N)	Probability o endoscopic relapse (%)	of Confidence limits (95%)
Pantoprazole 20 mg						
Start	203					
0–6 months	179	24	151	28	16	10-21
6–12 months	133	18	112	21	29	22-36
Pantoprazole 40 mg						
Start	193					
0–6 months	164	29	152	12	7	3-11
6–12 months	139	13	121	18	19	13-26

Table 3A. Evaluation of endoscopic remission and relapse

treatment with 10 mg omeprazole, compared with 12– 32% when 20 mg was used.^{4, 16, 28, 29, 31} A similar trend was seen with lansoprazole 15 mg and 30 mg when relapse rates of 21–46% and 10–23%, respectively, were reported.^{17, 21, 32} In a 12 month open-label study with a maintenance dose of 40 mg oral pantoprazole, the endoscopically-proven relapse was shown in 6% of patients.³³

In the present study, maintenance therapy with 20 mg or 40 mg pantoprazole administered for up to 12 months led to an endoscopic relapse of reflux oesophagitis in 29 and 19% of patients, respectively; the corresponding values for the symptomatic relapse rates were 21% in the 20 mg and 17% in the 40 mg

treatment group. Such values are in agreement with those found in a similar study performed in Germany and reported by Plein *et al.*³⁴ In that study, the endoscopic relapse rates of reflux oesophagitis after 12 months of treatment were 25 and 22%, for patients treated with 20 mg or 40 mg pantoprazole, respectively.³⁴

The results described here also indicate that, as with other proton pump inhibitors used in this clinical indication, the relapse rate is dependent on the therapeutic dose of pantoprazole.^{16, 29, 32, 34} The proportion of patients in the 20 mg pantoprazole treatment group who had an endoscopic relapse was lower than that shown for the group treated with a low dose (10 mg) of

Number of patient at risk during the study interval (<i>N</i>)	brop-outs and protocol violators (N)	Patients in remission completing the interval (N)	Patients with endoscopic relapse (<i>N</i>)	Probability o endoscopic relapse (%)	f Confidence limits (95%)
203					
191	12	178	13	7	3-10
165	13	152	13	14	9–19
135	17	130	5	17	12-23
121	9	115	6	21	15-28
193					
176	17	169	7	4	1 - 7
162	7	152	10	10	5-14
133	19	128	5	13	8-18
127	1	121	6	17	11-23
	Number of patient at risk during the study interval (N) 203 191 165 135 121 193 176 162 133 127	Number of patients at risk during the study Drop-outs and interval (N) protocol violators (N) 203 191 12 165 13 135 17 121 9 193 17 176 17 162 7 133 19 127 1	Number of patientsPatients inat risk duringremissionthe studyDrop-outs andcompletinginterval (N)protocol violators (N)the interval (N)2031121911217816513152135171301219115176171691627152133191281271121	Number of patientsPatients inat risk duringremissionPatients with endoscopicthe studyDrop-outs and protocol violators (N)completing the interval (N)endoscopic relapse (N)2031121781316513152131313517130512119317169716217617169716213319128512112711216	Number of patientsPatients inat risk duringremissionPatients withProbability of endoscopicthe studyDrop-outs andcompletingendoscopicendoscopicprotocol violators (N)the interval (N)relapse (N)relapse (%)20312178137191121781314135171305171219115621193171697416271521010133191285131271121617

Table 3B. Evaluation of symptomatic remission and relapse

Drop-outs and protocol violators represent the 'censored' patients indicated and defined in Table 2.

© 1999 Blackwell Science Ltd, Aliment Pharmacol Ther 13, 1481-1491

	Differences between treatment groups (90% CI)			
Treatment interval	Endoscopic relapse	Symptomatic relapse		
0–3 months		-3 (-7 to 1)		
3–6 months	-8 (-14 to -3)	-4 (-10 to 1)		
6–9 months		-4 (-10 to 2)		
9–12 months	-10 (-17 to -2)	-4 (-11 to 3)		

Table 4. Differences between the treatment groups, together with the 90% confidence limits, according to a Kaplan–Meier life-table analysis

The test for equivalence is a procedure consisting of two one-sided tests. For a one-sided test, the lower 90% confidence interval's limit provides the critical value. Hence, for the two one-sided tests the 90% confidence interval provides both critical values. Hypotheses being outside this interval can be rejected at the 5% level of significance. In the present study, only the lower limit was required, because only the 'at least equivalence' was tested for.

omeprazole,^{4, 16, 20, 28, 29, 31} and within the range reported for a low dose (15 mg) of lansoprazole.^{17, 20, 21, 32} It was noteworthy in our study that, of the patients who experienced endoscopic relapse, the proportion relapsing from the initial GERD grade II or III at diagnosis to grade I during the long-term maintenance treatment was similar in both treatment groups. Indeed, a worsening of the oesophagitis status was noticed for only one patient, for whom poor compliance with the 20 mg pantoprazole dose cannot be ruled out, and who had a relapse after 3 months from an initial grade II at diagnosis to grade (IV) (Figure 2).



Figure 3. Endoscopic remission rates for patients enrolled in the long-term maintenance therapy and treated with either 20 mg or 40 mg pantoprazole for up to 12 months. The data are presented as the Kaplan–Meier plot with 95% confidence limits.

© 1999 Blackwell Science Ltd, Aliment Pharmacol Ther 13, 1481–1491



Figure 4. Symptomatic remission rates for patients enrolled in the long-term maintenance therapy and treated with either 20 mg or 40 mg pantoprazole for up to 12 months. The data are presented as the Kaplan–Meier plot with 95% confidence limits.

The safety and tolerability of the treatment was monitored by the frequency and type of adverse events. According to the assessment made by the investigators, the number and the type of adverse events was similar between the two treatment groups (Table 5). The most common adverse events, affecting 1-3% of the total number of patients, included elevated serum concentration of liver enzymes, diarrhoea and abdominal pain; such results are in accord with other studies with pantoprazole^{10, 33, 34} or other proton pump inhibitors.^{15, 30}

As with other proton pump inhibitors, patients receiving pantoprazole as maintenance therapy had slightly elevated concentrations of serum gas-trin.^{12, 21, 33} Such elevation was regarded as not

Table 5. Frequency and causality assessment of adverse events

	Treatment group		
Parameter	Pantoprazole 20 mg	Pantoprazole 40 mg	
Number of patients enrolled in the study	203	193	
Number of <i>patients</i> with adverse events	53 (26%)	44 (23%)	
Number of adverse events	77	58	
Not related	64 (83%)	36 (62%)	
Possibly related	13 (17%)	20 (34%)	
Definitely related	0	2 (3%)	

The numbers in brackets represent percentages of the respective parameter.

clinically relevant, as gastrin levels tend to return to normal after the discontinuation of treatment with proton pump inhibitors.³⁵ Moreover, regular monitoring of serum gastrin concentration during therapy with proton pump inhibitors has been described as unnecessary by others.³⁶

In conclusion, the present long-term maintenance study demonstrates that a once daily dose of 20 mg or 40 mg pantoprazole is safe and well tolerated and that both doses are therapeutically 'at least equivalent' in preventing symptomatic and endoscopic relapse in patients with healed reflux oesophagitis. Because pantoprazole 20 mg can maintain the majority of patients free of relapse, this dose could be regarded as a good start for maintenance therapy.

For those patients who do relapse while receiving 20 mg pantoprazole, it may be necessary to regain healing with a short-term course (4–8 weeks) of 40 mg pantoprazole before recommencing with the maintenance dose of 20 mg. Such an approach would minimize the patients' exposure to the drug and potentially lower the cost of the therapy.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the following investigators from The European Pantoprazole Study Group for their participation in the study. Belgium: Drs L. E. C. Lepoutre (Aalst), G. K. M. Robaevs (Genk), A. Nakad (Tournai), V. Gillard (Liege), R. Fiasse (Bruxelles), P. A. R. Pelckmans (Edegem), J. P. F. Janssens (Leuven); France: Drs H. Baumann (Strasbourg Cedex), J.-P. Desechalliers (Elbeuf), D. Cattan (Villeneuve), M. G. M. Doffoel (Strasbourg), E. Fort (Chateauroux), J. I. Gilson (Beziers Cedex), P. Guivarch (Castres), J. P. Ramain (Blois), H. Gouerou (Brest Cedex), J.-F. Rev (Saint Laurent Du Var), H. Michel (Montpellier Cedex 5), M. Mignon (Paris), G. Naudin (Paris Cedex 12), D. Sondag (Mulhouse), E. Vaucher (Narbonne Cedex); Italy: Drs E. Camarri (Grosseto), A. Cardelli (Rimini), R. Corinaldesi (Bologna), G. Dobrilla (Bolzano), A. Ferrarri (Torino), S. Fiorucci (Perugia), R. Galeazzi (Ancona), G. Gatto (Palermo), G. Mazzacca (Napoli), F. Mazzeo (Piacenza), M. Miglioli (Bologna), G. Minoli (Como), A. Tittobello (Milano), M. Valentini (Aviano, Pordenone); the Netherlands: Drs J. A. Beker (Leidschendam), A. A. M. Geraedts (Amsterdam), W. W. Meyer (Den Helder), R. J. T. Ouwendijk (Rotterdam), H. Sikkens (Blaricum), B. D. Westerveld (Zwolle), A. M.

H. Wetzels (Stadskanaal); and Dr Kathy B. Thomas (Byk Gulden, Konstanz, Germany), for helpful suggestions during the preparation and editing of this manuscript.

This study was supported by a grant from Nycomed Pharma, Roskilde, Denmark and Byk Gulden Pharmaceuticals, Konstanz, Germany.

REFERENCES

- 1 Penston JG, Pounder RE. A survey of dyspepsia in Great Britain. Aliment Pharmacol Ther 1996; 10: 83–9.
- 2 Locke GR, Talley NJ, Fett SL, *et al*. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112: 1448–56.
- 3 Richter JE. Long-term management of gastroesophageal reflux disease and its complications. Am J Gastroenterol 1997; 92: S30–4.
- 4 Vigneri S, Termini R, Leandro G, *et al.* A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med 1995; 333: 1106–10.
- 5 Moss SF, Arnold R, Tytgat GNJ, et al. Consensus statement for management of gastroesophageal reflux disease. J Clin Gastroenterol 1998; 27: 6–12.
- 6 Savary M, Miller G (eds). The esophagus. In: Handbook and Atlas of Endoscopy. Switzerland: Verlag Gassman AG, 1978: 119–205.
- 7 Mössner J, Hölscher AH, Herz R, *et al.* A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther 1995; 9: 321–6.
- 8 Corinaldesi R, Valentini M, Belaiche J, *et al.* Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. Aliment Pharmacol Ther 1995; 9: 667–71.
- 9 Koop H, Schepp W, Dammann HG, et al. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. J Clin Gastroenterol 1995; 20: 192–5.
- 10 Fitton A, Wiseman L. Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs 1996; 51: 460–82.
- 11 Chiba N, De Gara CJ, Wilkinson JM, *et al.* Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997; 112: 1798–810.
- 12 Chiba N. Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: a systematic overview. Can J Gastroenterol 1997; 11(Suppl. B): B66–73.
- 13 Boyce HW. Therapeutic approaches to healing esophagitis. Am J Gastroenterol 1997; 92: S22–7.
- 14 Fennerty MB, Lieberman D. H2-receptor antagonists in the treatment of complicated gastroesophageal reflux disease: 'for whom the bell tolls'. Gastroenterology 1994; 107: 1545–8.
- 15 Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors. Pharmacology and rationale for use in gastrointestinal disorders. Drugs 1998; 56: 307–35.

- 16 Lundell L. Long-term treatment of gastro-oesophageal reflux disease with omeprazole. Scand J Gastroenterol Suppl. 1994; 201: 74–8.
- 17 Robinson M, Lanza F, Avner D, *et al.* Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124: 859–67.
- 18 Reynolds JC. Influence of pathophysiology, severity, and cost on the medical management of gastroesophageal reflux disease. Am J Health Syst Pharm 1996; 53: S5–12.
- 19 Bate CM, Green JR, Axon AT, *et al.* Omeprazole is more effective than cimetidine for the relief of all grades of gastrooesophageal reflux disease-associated heartburn, irrespective of the presence or absence of endoscopic oesophagitis. Aliment Pharmacol Ther 1997; 11: 755–63.
- 20 Johnson DA. Medical therapy of GERD: current state of the art. Hosp Pract 1996; 31: 135–48.
- 21 Gough AL, Long RG, Cooper BT, *et al.* Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. Aliment Pharmacol Ther 1996; 10: 529–39.
- 22 Venables TL, Newland RD, Patel AC, *et al.* Maintenance treatment for gastro-oesophageal reflux disease. A placebocontrolled evaluation of 10 milligrams omeprazole once daily in general practice. Scand J Gastroenterol 1997; 32: 627–32.
- 23 Hatlebakk JG, Berstad A. Prognostic factors for relapse of reflux oesophagitis and symptoms during 12 months of therapy with lansoprazole. Aliment Pharmacol Ther 1997; 11: 1093–9.
- 24 Steinijans VW, Huber R, Hartmann M, *et al.* Lack of pantoprazole drug interactions in man: an updated review. Int J Clin Pharmacol Ther 1996; 34: S31–50.
- 25 Johansson KE, Boeryd B, Johansson K, *et al.* Double-blind crossover study of ranitidine and placebo in gastro-oesophageal reflux disease. Scand J Gastroenterol 1986; 21: 769–78.
- 26 Havelund T, Laursen LS, Lauritsen K. Efficacy of omeprazole in lower grades of gastro-oesophageal reflux disease. Scand J Gastroenterol Suppl. 1994; 201: 69–73.

- 27 Bardhan KD. Duodenal ulcer and gastroesophageal reflux disease today: long-term therapy—a sideways glance. Yale J Biol Med 1996; 69: 211–24.
- 28 Hallerbäck B, Unge P, Carling L, *et al.* Omeprazole or ranitidine in long-term treatment of reflux esophagitis. The Scandinavian Clinics for United Research Group. Gastroenterology 1994; 107: 1305–11.
- 29 Bate CM, Booth SN, Crowe JP, et al. Omeprazole 10 mg or 20 mg once daily in the prevention of recurrence of reflux oesophagitis. Solo Investigator Group. Gut 1995; 36: 492–8.
- 30 Laursen LS, Havelund T, Bondesen S, et al. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomized dose-finding study. Scand J Gastroenterol 1995; 30: 839–46.
- 31 Dent J, Yeomans ND, Mackinnon M, et al. Omeprazole v ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. Gut 1994; 35: 590–8.
- 32 Hatlebakk JG, Berstad A. Lansoprazole 15 and 30 mg daily in maintaining healing and symptom relief in patients with reflux oesophagitis. Aliment Pharmacol Ther 1997; 11: 365–72.
- 33 Mössner J, Koop H, Porst H, *et al.* One-year prophylactic efficacy and safety of pantoprazole in controlling gastro-oesophageal reflux in patients with healed reflux oesophagitis. Aliment Pharmacol Ther 1997; 11: 1087–92.
- 34 Plein K, Hotz J, Wurzer H, *et al.* Pantoprazole 20 mg is an effective maintenance therapy for patients with gastro-oeso-phageal reflux disease. Eur J Gastroenterol Hepatol 1999, in press.
- 35 Freston JW, Malagelada JR, Petersen H, *et al*. Critical issues in the management of gastroesophageal reflux disease. Eur J Gastroenterol Hepatol 1995; 7: 577–86.
- 36 Beck IT, Champion MC, Lemire S, *et al.* The Second Canadian Consensus Conference on the Management of Patients with Gastroesophageal Reflux Disease. Can J Gastroenterol 1997; 11(Suppl. B): B7–20.