A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial

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Accepted for publication 22 January 1995

SUMMARY

Background: Pantoprazole is a new substituted benzimidazole which is a potent inhibitor of gastric acid secretion by its action upon H⁺,K⁺-ATPase. Aim: To compare pantoprazole 40 mg with omeprazole 20 mg as once daily dosing in the treatment of reflux oesophagitis (grades II and III). Methods: This double-blind, randomized, multicentre study included 286 patients. Patients were re-endoscoped after 4 weeks, and continued to receive a further 4 weeks of treatment if they were not healed at this time. Results: After 4 weeks of treatment, complete healing occurred in 126/170 (74%) patients in the pantoprazole group and in 67/86 (78%) patients in the omeprazole group (per-protocol analysis). At 8 weeks, the corresponding healing rates were 153/170 (90%) and 81/86 (94%). The differences between the treatment groups were not significant (P = 0.57 and 0.34). Improvement in the principal symptoms of reflux oesophagitis was also very similar between the treatment groups, with 59% and 69% at 2 weeks, and 83% and 86% at 4 weeks, respectively, being free from any individual symptom. Both treatments were well tolerated. Conclusions: This study has shown pantoprazole and omeprazole to be similarly effective and well tolerated in the treatment of mild to moderate reflux oesophagitis.

INTRODUCTION

Pantoprazole is a new substituted benzimidazole which selectively inhibits the gastric H⁺,K⁺-ATPase, blocking the final step in acid secretion.¹ Like other compounds of the same class, pantoprazole has a profound antisecretory action as demonstrated by its inhibition of pentagastrin-stimulated gastric acid secretion in man following both single and repeated intravenous²,³ and oral dosing.⁴ It has been shown to be at least as effective as omeprazole in increasing intragastric pH,⁵ and no clinically relevant changes in laboratory or cardiovascular parameters were observed in clinical phase I studies.⁶-⁸ Pantoprazole is metabolized mainly in the liver via the cytochrome P-450 system; it has been shown to have less potential for interaction with this system than omeprazole,¹ and also to have no clinically relevant effect on steady-state theophylline⁶ and diazepam⁹ serum concentrations in man.

A number of studies have confirmed the efficacy of this class of drugs in the treatment of duodenal and gastric ulceration,⁶-⁹ with the substituted benzimidazoles generally producing more rapid healing than the H₂-receptor antagonists. The most important factor in the pathophysiology of reflux oesophagitis is the repeated exposure of the oesophageal mucosa to gastric acid. Therefore, the substituted benzimidazoles, with their more profound inhibition of acid secretion, would be expected to be efficacious in this disease. Indeed, omeprazole has been shown to be highly effective and superior to ranitidine in the treatment of reflux oesophagitis.¹⁰-¹³ Pantoprazole has also been shown to be superior to ranitidine in the
rate of healing of reflux oesophagitis. This study was designed to investigate the efficacy and safety of a once-daily dose of pantoprazole (40 mg) in comparison with omeprazole (20 mg) in patients with reflux oesophagitis.

PATIENTS AND METHODS

The study was a randomized, multicentre, double-blind, parallel-group study of pantoprazole 40 mg compared with omeprazole 20 mg. Patients were entered to the study from 44 centres in Germany. The approval of an independent Ethics Committee was sought prior to initiation of the study, and all patients provided informed consent, either written or signed by a witness.

Patients eligible for inclusion in the study were male or female, aged at least 18 years. They had reflux oesophagitis, grade II or III according to Savary–Miller, endoscopically diagnosed within 3 days of starting study medication. In addition, patients had at least one of the following key symptoms of gastro-oesophageal reflux disease: acid regurgitation without nausea, heartburn, or pain on swallowing.

Patients with peptic ulcer, reflux oesophagitis grades I or IV, a history of Zollinger–Ellison syndrome, or patients who had had previous surgery of the oesophagus or gastrointestinal tract were excluded. Treatment with substituted benzimidazoles in the 30 days prior to study entry was prohibited, as was concomitant therapy with any drugs whose absorption was pH-dependent or drugs which could interact with substituted benzimidazoles. Other exclusion criteria included severe concomitant disease, pregnancy, lactation, lack of reliable contraception in women of child-bearing age, and clinically relevant deviations from the normal range in screening laboratory studies.

Patients received one of the study treatments according to a computer-generated randomization list. The ratio of the treatments was unbalanced, 2:1 in favour of pantoprazole. All study medication was taken once daily, in the morning before breakfast, for the entire duration of the study (4 or 8 weeks). Patients received the matching placebo of the comparator medication in a double-blind fashion, and no rescue medication for the relief of symptoms of reflux disease was permitted.

Patients were assessed endoscopically on entry to the study and after 4 weeks. If the oesophageal lesion was not completely healed (complete re-epithelialization) at this time, patients received treatment for a further 4 weeks and endoscopical examination was repeated at the end of this period. Additional visits, without endoscopical examination, took place after 2 and (if appropriate) after 6 weeks of treatment.

The severity of the principal symptoms of gastro-oesophageal reflux disease, namely acid regurgitation without nausea, heartburn, or pain on swallowing, were recorded at each visit as absent, mild, moderate, or severe. Other gastrointestinal symptoms, namely epigastric pain, retrosternal pain, retrosternal tightness, belching, nausea, retching or vomiting, were recorded according to the same scale. Patients also kept a daily diary card of their symptoms.

The safety of the study medications was assessed by the occurrence of adverse events, recorded at each visit, and by laboratory evaluations (haematology, clinical chemistry, urinalysis) at 4 weeks and, if appropriate, 8 weeks. Fasting serum gastrin concentrations were determined by 125I-radioimmunoassay (Becton Dickinson GmbH, Heidelberg, Germany).

The sample size for the study was calculated to detect a difference of 18% in the healing rates between the treatment groups (62%; 80%; Fisher's exact test); 240 patients were required to detect this difference (160 pantoprazole: 80 omeprazole) based on a two-sided test at the 5% level of significance and a power of approximately 80%.

The primary measures of efficacy were the complete healing of the oesophageal lesion after 4 weeks, and after 8 weeks in patients unhealed at 4 weeks, and improvement in the principal symptoms of reflux disease. Healing of the lesion was compared between the two groups using the Cochran–Mantel Haenszel method, and the time to healing was evaluated using Uleman's U-test. The sum of the scores for the individual principal symptoms of reflux disease and the total scores were compared between the treatment groups using Uleman's U-test. In addition, complete freedom from any of the principal symptoms at 2 and 4 weeks was compared using Fisher's exact test.

Secondary measures of efficacy were the assessment of the other gastrointestinal symptoms and the diary card data. The mean score sums were calculated and plotted for each symptom, and the time to complete relief (1 day and 3 consecutive days) of symptoms recorded on the diary cards was compared between groups using Uleman's U-test. Only data from the first 4 weeks of the study were used in the analysis of symptoms.

The main statistical analysis was on a per-protocol basis and excluded any patients not meeting agreed protocol
criteria and patients who withdrew from the study for reasons not related to the study medication. Patients with visit dates within −2 and +5 days of the study schedule were included in the per-protocol analysis. An intention-to-treat analysis of healing rates, which included all protocol violators as unhealed cases, was also performed. All patients were included in the safety analysis.

RESULTS

A total of 286 patients entered the study; 191 received pantoprazole and 95 omeprazole. Thirty patients were excluded from the analysis according to the protocol (three had their initial endoscopic examination more than 3 days prior to starting study medication, three were excluded because of adverse events not related to the study medication, one was non-compliant and 23 did not attend or attended outside the allowed visit schedule). Two hundred and fifty-six patients were therefore included in the per-protocol analysis: 170 received pantoprazole 40 mg once daily and 86 received omeprazole 20 mg once daily. Three of these patients were withdrawn prematurely from the study, two owing to adverse events (one in each treatment group) and one patient in the pantoprazole group because of lack of efficacy.

The treatment groups were comparable at baseline (Table 1).

Table 1. Baseline entry characteristics (intention-to-treat population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pantoprazole (n = 191)</th>
<th>Omeprazole (n = 95)</th>
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<tbody>
<tr>
<td>Males (%)</td>
<td>133 (70)</td>
<td>66 (69)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>58 (30)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>53 (19-89)</td>
<td>55 (21-81)</td>
</tr>
<tr>
<td>Grade of reflux oesophagitis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>155 (81)</td>
<td>73 (77)</td>
</tr>
<tr>
<td>III</td>
<td>36 (19)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>No previous history of reflux oesophagitis (%)</td>
<td>107 (56)</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Number of previous episodes of reflux oesophagitis (%)</td>
<td>9 (5)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>1</td>
<td>75 (39)</td>
<td>34 (36)</td>
</tr>
<tr>
<td>Presence of principal symptoms (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td>186 (97)</td>
<td>95 (100)</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>171 (90)</td>
<td>91 (96)</td>
</tr>
<tr>
<td>Pain on swallowing</td>
<td>83 (43)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>51 (27)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Alcohol consumption (%)</td>
<td>32 (17)</td>
<td>21 (22)</td>
</tr>
</tbody>
</table>

* Endoscopically diagnosed.

The healing rates are presented in Figure 1. After 4 weeks of treatment, complete healing occurred in 126/170 (74%) patients in the pantoprazole group and in 67/86 (78%) patients in the omeprazole group. After 8 weeks, the cumulative healing rates were 153/70 (90%) and 81/86 (94%) in the pantoprazole and omeprazole groups, respectively. The differences between the treatment groups were not significant at 4 weeks (P = 0.57) or at 8 weeks (P = 0.34, Cochran–Mantel Haenszel analysis). The differences between the treatment groups were also not significant in the intention-to-treat analysis. In terms of time to healing, there was no significant difference between the treatment groups (P = 0.45, Uleman’s U-test). Patients with grade III oesophagitis healed more slowly than those with grade II oesophagitis; at 4 weeks, 78% and 85% of patients with grade II oesophagitis in the pantoprazole and omeprazole groups, respectively, had healed, compared with only 59% and 53% of patients with grade III oesophagitis. However, by 8 weeks the healing rates were very similar.

With regard to the principal symptoms—heartburn,
Table 2. Serum gastrin levels* and median changes on treatment (ng/L)

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole 40 mg</th>
<th>Omeprazole 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>n</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>(68% range)</td>
<td>(34 to 83)</td>
</tr>
<tr>
<td>Week 4</td>
<td>n</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>median change</td>
<td>+17</td>
</tr>
<tr>
<td></td>
<td>(68% range)</td>
<td>(-11 to +60)</td>
</tr>
<tr>
<td>Week 8</td>
<td>n</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>median change</td>
<td>+19</td>
</tr>
<tr>
<td></td>
<td>(68% range)</td>
<td>(-17 to +134)</td>
</tr>
</tbody>
</table>

* Normal range = 0-100 ng/L.

either 1 day or 3 consecutive days was not statistically significant (P = 0.43 and 0.34, respectively).

Safety

Both treatments were well tolerated. Twenty-three of 191 patients in the pantoprazole group (12%) and 8/95 patients in the omeprazole group (8%) reported adverse events (intention-to-treat analysis). The majority of events were considered not to be related to the study treatment. Nine patients in the pantoprazole group and three patients in omeprazole group experienced events which were considered possibly or definitely related to the study treatment. For one event on pantoprazole and six events (in two patients) on omeprazole, no assessment was given. No serious adverse events were reported. Only one patient in each treatment group was withdrawn from the study because of adverse events related to the study medication.

Routine clinical laboratory tests after 4 and 8 weeks of treatment did not indicate any trends from baseline within individual parameters. Results for individual patients which may have been considered a clinically relevant change were generally unlikely to have been related to the study treatment; only one change was reported as an adverse event. This patient’s alkaline phosphatase was significantly raised at both 4 and 6 weeks compared with the baseline value. The patient was withdrawn from the study, and the value had returned to within the normal range 2 weeks later; the elevation was considered to be possibly related to the study treatment (omeprazole).
Increases in serum gastrin concentration were observed in both treatment groups after 4 weeks (Table 2). The median changes from baseline after 8 weeks were very similar to those after 4 weeks in both treatment groups.

DISCUSSION

Until the introduction of the substituted benzimidazoles, \(H_2\)-receptor antagonists were the mainstay of treatment for acid-related disorders; however, their efficacy in the treatment of gastro-oesophageal reflux disease is not optimal.\(^{15}\) The substituted benzimidazoles produce a more profound inhibition of gastric acid than do the \(H_2\)-receptor antagonists,\(^{14}\) and indeed, have been shown to have a clinical advantage in the treatment of both duodenal and gastric ulceration,\(^{8}\) and gastro-oesophageal reflux disease.\(^{11,14,17}\)

In this study, healing rates in reflux oesophagitis were 74% and 78% at 4 weeks with pantoprazole and omeprazole, respectively. At 8 weeks, the corresponding healing rates were 90% and 94%. The difference in healing rates was not statistically significant. These results are similar to those reported in previous studies with omeprazole.\(^{8}\) In this study, patients with more severe oesophagitis (grade III) did not respond as well by 4 weeks as those with grade II oesophagitis. However, by 8 weeks the healing rates were very similar, indicating that pantoprazole and omeprazole are effective in more severe cases of oesophagitis, but that a longer course of treatment may be required.

The patients in this study also responded well symptomatically, with 59% of patients being free from all the principal symptoms, namely acid regurgitation, heartburn and pain on swallowing, after 2 weeks. After 4 weeks, 83% of patients were free from these symptoms. Again, the differences between the treatment groups were not statistically significant, suggesting that pantoprazole is comparable in efficacy to omeprazole in the treatment of both the endoscopic and symptomatic manifestations of reflux oesophagitis.

The study treatments were well tolerated: 8% and 12% of patients in the omeprazole and pantoprazole groups, respectively, reported adverse events, the majority of which were not considered to be causally related to the study treatment. Only one patient in each treatment group was withdrawn prematurely because of an adverse event. Changes in serum gastrin concentrations from baseline were very similar in both treatment groups, and increased only marginally after the 2-week assessment.

The median changes were in the order of 20 ng/L and, as previously demonstrated, are unlikely to be associated with any clinically relevant changes in the enterochromaffin-like cells of these patients.\(^{18}\)

In summary, pantoprazole 40 mg daily has been shown to be effective and well-tolerated in the treatment of reflux oesophagitis; it is similar in efficacy to another substituted benzimidazole, omeprazole, in the treatment of both the endoscopic signs and the symptoms of reflux oesophagitis.

ACKNOWLEDGEMENTS

We would like to thank the following investigators who contributed patients to this study: B. Adami, Alzey; H. Ahrens, Paderborn; H. Bouzo, Augsburg; H.-P. Brackmann, Bad Lippspringe; H. Brinkhoff, Stuhlr; G. Büttner, Berlin; H. Daake, Wiesbaden; A. Dettmer, Munich; K. Dietrich, Saarbrücken; W. Fuchs, Bensheim; H.-J. Gütz, Berlin Buch; H. Hebbeln, Itzehoe; J. Hotz, Celle; W. Hüttemann, Aachen; M. Kirchhof, Hamburg; H. Koop, Marburg; K.-H. Kratzsch, Chemnitz; H. Kunert, Freiburg i. Br.; M. Kunze, Suhl; M. Köslng, Bremen; U. B. Mairose, Wülfrath; E. Meier, Amberg; S. E. Miederer, Bielefeld; D. Mildner, Zepernick; W. Mittmann, Potsdam; B. Müller, Merseburg; A. Naumburger, Berlin; H. Porst, Dresden; D. Raps, Schopfheim; I. Rehmann, Lippstadt; H. G. Rohner, Schwerte; G. Rosprich, Saarbrücken; W. Schmeisser, Reutlingen; H. Schönekas, Nürnberg; E. Schütz, Regensburg; B. Simon, Schwetzingen; G. Tangerding, Wangen; K. Uhlig, Berlin; R. Vogt, Mannheim; H. Wübboldng, Damme; and J. Zeus, Erlangen.

REFERENCES


