Pantoprazole versus lansoprazole in French patients with reflux esophagitis

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SUMMARY

Objectives — The aim of this study was to compare the efficacy of pantoprazole 40 mg and lansoprazole 30 mg given for 4 to 8 weeks on endoscopic healing and symptom relief in grade II-III reflux esophagitis patients (according to Savary-Miller classification).

Methods — Four hundred and sixty one patients were included (pantoprazole n = 226, lansoprazole n = 235) in this prospective, randomized, multicenter double-blind study. Endoscopic control was performed at 4 weeks and at 8 weeks if esophagitis was not healed.

Results — In the intention-to-treat analysis, the healing rates at 4 weeks were 81 and 80% in the pantoprazole and lansoprazole groups, respectively (NS), 90 and 86% at 8 weeks (NS). In the per-protocol analysis, the healing rates at 4 weeks were 86% in the 2 groups and at 8 weeks 97% in the pantoprazole group and 93% in the lansoprazole group (NS). The heartburn relief rates at day 14 were 88% and 86% in the pantoprazole and lansoprazole groups, respectively. Only esophagitis grade at entry was shown to be a predictive factor for healing at 4 weeks (P < 0.0001).

Conclusion — This study showed that pantoprazole 40 mg once daily is as effective and well tolerated as lansoprazole 30 mg once daily in the treatment of grade II-III acute reflux esophagitis.

Key words: Reflux esophagitis. Gastro-esophageal reflux. Pantoprazole. Lansoprazole.

RéSUMÉ

Comparaison du pantoprazole 40 mg et du lansoprazole 30 mg dans l’œsophagite par reflux gastro-œsophagien

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(Gastroenterol Clin Biol 2001;25:245-250)

Objectifs — Le but de ce travail était de comparer l’efficacité du pantoprazole 40 mg/j à celle du lansoprazole 30 mg/j sur la cicatrisation et le soulagement des symptômes de l’œsophagite par reflux de grade II ou III selon la classification de Savary-Miller.

Méthodes — Quatre cent soixante et un malades étaient inclus dans un essai prospectif, multicentrique, randomisé et conduit en double aveugle. Un contrôle endoscopique était réalisé à 4 semaines et éventuellement répété à 8 semaines en l’absence de cicatrisation.

Résultats — L’analyse « en intention de traiter » montrait un taux de cicatrisation à 4 semaines de 81 % dans le groupe pantoprazole et de 80 % dans le groupe lansoprazole (NS), et un taux de cicatrisation à 8 semaines de 90 % dans le groupe pantoprazole et de 86 % dans le groupe lansoprazole (NS). L’analyse des malades « en per protocol » montrait un taux de cicatrisation de 86 % à 4 semaines, identique dans les 2 groupes, et un taux de cicatrisation à 8 semaines de 97 % dans le groupe pantoprazole et de 93 % dans le groupe lansoprazole (NS). Le soulagement du pyrosis au 14e j concernait 88 % des malades dans le groupe pantoprazole et 86 % de ceux du groupe lansoprazole. Seul le stade endoscopique initial de l’œsophagite était un facteur pronostique de cicatrisation à 4 semaines (P = 0,0001).

Conclusion — Le pantoprazole 40 mg a une efficacité et une tolérance similaires à celles du lansoprazole 30 mg dans le traitement de l’œsophagite par reflux de stade II-III.


Gastro-oesophageal reflux disease (GERD) is a very common and recurrent disorder of the upper digestive tract. The principal factors in the development and perpetuation of symptoms and esophageal lesions are the duration of exposure to acid secretion, and the amount and concentration of gastric acid in the refluxed material.

Proton pump inhibitors (PPIs) have proved to be significantly more effective than H₂-receptor antagonists for relieving reflux symptoms and healing esophagitis [1] even when a high dose of ranitidine is used [2]. However, published results are conflicting as to whether any differences in efficacy exist between omeprazole, lansoprazole and pantoprazole for treating reflux esophagitis [3, 4]. Compared with omeprazole 20 mg, lansoprazole 30 mg was shown to be similarly effective with respect to esophageal healing, but to provide superior symptomatic relief, primarily early in treatment [5].

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Pantoprazole is a new proton pump inhibitor which, used at the standard dose of 40 mg once daily (od), was reported to be safe and not to significantly interfere with the metabolism of other
drug abuse and clinically relevant deviations from the normal range in the following laboratory parameters: creatinine > 300 mmol/L, ASAT and/or ALAT > 2x the normal range. Concomitant therapy with anti-ulcer medications such as PPIs (other than study medications), H₂-receptor antagonists, prokinetic agents, sucralfate or mucosal protective agents (prostaglandins, antacids or alginate) was not allowed.

The study protocol was approved by the “Comité Consultatif de Protection des Personnes se prêtant à une Recherche Biomédicale (CCPRPB)” of Picardie. Signed informed consent was obtained from all patients prior to enrolment in the trial. On-site checks of the Case Report Forms and source data verification were performed by Clinical Research Associates (CRAs) of the Department of Clinical Research of Byk France.

**Efficacy evaluation**

Efficacy of the trial medication was assessed by endoscopy after 4 weeks of treatment and after 8 weeks if lesions were not completely healed after 4 weeks.

The symptoms heartburn, acid regurgitation and pain on swallowing were recorded on day 0, 14, 28 and if necessary on days 42 and 56. These symptoms were scored on a 4-point scale, ranging from 0 (none) through 1 (minimal) and 2 (moderate) to 3 (severe) and a reflux score was calculated [14]. If at least one of these 3 symptoms was lacking, the predominant reflux symptoms were recorded in accordance with the same scale. The presence of symptoms was also evaluated with a diary card given to the patients. Speed of reflux symptom relief was measured by the number of days between the start of treatment and complete relief according to the patient. Relief time was defined as the first day of 3 consecutive days without symptoms.

**Safety evaluation**

Routine laboratory tests were performed prior to treatment and after 4 weeks. In addition, tests were repeated after 8 weeks if the esophagitis was not completely healed after 4 weeks. Laboratory parameters included hematology (hemoglobin, red blood cells, white blood cells and platelets count) and biochemistry (glucose, creatinine, total bilirubin, ASAT, ALAT, alkaline phosphatase), and were performed in the fasted state. Patients had to be withdrawn if there were clinically significant deviations from the normal range of the laboratory parameters at the initial examination.

At each visit, a general physical examination was performed and patients were questioned for general symptoms. Patients were also encouraged to use their diary card to record any adverse event in the “other” section. Description included date of onset, duration of the event, intensity, corrective measures and outcome. Degrees of severity of adverse events were assessed on a scale from 0 to 3. The causal relationship between the study medication and the adverse event was assessed by the investigator differentiating between four categories, i.e. “no relation”, “unlikely relation”, “likely relation” and “definite relation”.

**Statistical analysis**

The main evaluation criterion of efficacy was the endoscopic healing rate after 4 weeks of treatment assessed according to the Fisher’s exact test. Secondary efficacy parameters were the cumulative endoscopic healing rate after 8 weeks assessed using the Fisher’s exact test as well as rapidity of symptom relief and the symptom resolution rates. The rapidity of symptom relief was calculated with the Kaplan-Meier’s method and differences between curves were tested by the log-rank test. The score sums for the individual key symptoms (heartburn, acid regurgitation and pain on swallowing) and the total score sum at 2 and 4 weeks were compared by the Ulemann’s non-parametric test. The relation between the total score sum at day 0 and the time until relieving was assessed using the Cox’s model. An analysis of the predictive factors for healing at 4 weeks and symptoms relief at day 14 was performed using the logistic regression method. The main statistical analysis was conducted on the per-protocol population and excluded all patients not meeting protocol criteria and patients who withdrew from the study for reasons not related to the study medication. An intention-to-treat analysis which included all protocol violators as unhealed cases was also performed. All randomized patients were included in the safety analysis. Two-sided tests and the 5% level of significance were used throughout. Statistical analysis was performed using the statistical package SAS, version 6.12 by RCTs, Lyon, France.
Results

A total of 461 patients were included: 225 received pantoprazole 40 mg od and 236 lansoprazole 30 mg od. The intention-to-treat population included 76 protocol violators who were not replaced: disrespect of inclusion criteria, n = 5; unauthorized concomitant medication, n = 3; no attendance to control visits, n = 42; premature termination of the study, n = 18; bad compliance, n = 6; breaking of the blinding, n = 2 (figure 1). The distribution of gender, age, weight, height, smoking and alcohol intake as well as distribution of stages of esophagitis, distribution of previous recurrences of esophagitis and key symptoms were very similar in the 2 treatment groups (table I). The tablets/capsules counts and crosschecks indicated that compliance was generally good. Minor deviations or failure to return the unused medication did occur in some patients. However, these patients were accepted in the per-protocol analysis.

Endoscopic healing

Both the intention-to-treat and per-protocol analyses showed that endoscopic healing occurred in both treatment groups after 4 and 8 weeks with no statistical difference between pantoprazole and lansoprazole based on the calculation of the 90% confidence intervals of the common odds ratio for the healing rate. In the comparative intention-to-treat analysis, where all protocol violation were included with the last observation carried forward, healing rates were 184/226 (81%) in the pantoprazole group and 189/235 (80%) in the lansoprazole group after 4 weeks. After 8 weeks treatment, these rates increased to 203/226 (90%) and 201/235 (86%), respectively. According to the per-protocol analysis, complete endoscopically proven healing was found in 160/187 (86%) patients of the pantoprazole group and in 170/198 (86%) patients of the lansoprazole group after 4 weeks.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pantoprazole (n = 225)</th>
<th>Lansoprazole (n = 236)</th>
<th>Total (n = 461)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± s.d.)</td>
<td>53 ± 14.5</td>
<td>55 ± 14.7</td>
<td>54 ± 14.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Height (cm, mean ± s.d.)</td>
<td>170 ± 8.9</td>
<td>170 ± 8.3</td>
<td>170 ± 8.6</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg, mean ± s.d.)</td>
<td>77 ± 12.6</td>
<td>76 ± 12.2</td>
<td>77 ± 12.4</td>
<td>0.57</td>
</tr>
<tr>
<td>Sex male/female (% male)</td>
<td>165/60 (73 %)</td>
<td>178/58 (75 %)</td>
<td>343/118 (74 %)</td>
<td>0.61</td>
</tr>
<tr>
<td>Smoking smoker/non smoker (% smoker)</td>
<td>45/180 (20 %)</td>
<td>56/180 (24 %)</td>
<td>101/360 (22 %)</td>
<td>0.62</td>
</tr>
<tr>
<td>Alcohol Daily/Not daily (%)</td>
<td>45/180 (20 %)</td>
<td>47/189 (20 %)</td>
<td>92/369 (20 %)</td>
<td>0.98</td>
</tr>
<tr>
<td>Drug addiction None, n (%)</td>
<td>225 (100 %)</td>
<td>236 (100 %)</td>
<td>461 (100 %)</td>
<td>—</td>
</tr>
<tr>
<td>DeMeester score Median (min-max)</td>
<td>3 (0-8)</td>
<td>3 (0-9)</td>
<td>3 (0-9)</td>
<td>0.26</td>
</tr>
<tr>
<td>DeMeester score = 0 N (%)</td>
<td>11 (5 %)</td>
<td>8 (3 %)</td>
<td>19 (4 %)</td>
<td>—</td>
</tr>
<tr>
<td>Heartburn N (%)</td>
<td>222 (90 %)</td>
<td>223 (94 %)</td>
<td>425 (92 %)</td>
<td>0.21</td>
</tr>
<tr>
<td>Acid regurgitation N (%)</td>
<td>163 (72 %)</td>
<td>178 (75 %)</td>
<td>341 (74 %)</td>
<td>0.71</td>
</tr>
<tr>
<td>Pain on swallowing N (%)</td>
<td>79 (35 %)</td>
<td>70 (30 %)</td>
<td>149 (32 %)</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of symptoms First episode, n</td>
<td>31 (14 %)</td>
<td>26 (11 %)</td>
<td>57 (12 %)</td>
<td>0.72</td>
</tr>
<tr>
<td>Any esophageal findings at prior endoscopy, n (%)</td>
<td>126 (57 %)</td>
<td>139 (59 %)</td>
<td>265 (58 %)</td>
<td>—</td>
</tr>
<tr>
<td>Esophagitis grade II/III N/N (% grade II)</td>
<td>186/39 (83 %)</td>
<td>197/39 (83 %)</td>
<td>383/78 (83 %)</td>
<td>—</td>
</tr>
</tbody>
</table>
of treatment (figure 2). After 8 weeks treatment, the cumulative healing rates were 175/180 (97%) and 182/195 (93%) in the pantoprazole and lansoprazole groups, respectively.

**Symptom relief**

At study inclusion, the key symptoms heartburn, acid regurgitation and pain on swallowing were reported by 90, 72 and 35% of the patients in the pantoprazole group and 94, 75 and 30% of the patients in the lansoprazole group, respectively. The duration of symptoms of reflux esophagitis was similar in both groups (P > 0.05, U-test) (table I).

A marked relief from these symptoms was observed in both groups as early as 2 weeks with a further improvement after 4 weeks of treatment. After 2 weeks of treatment (intention-to-treat analysis) 77% of the patients in the pantoprazole group and 73% in the lansoprazole group were completely free from any of the key symptoms. After 4 weeks, the corresponding rates were 83% for both groups (table II). Comparison of the 3 key symptoms and the individual key symptoms at 2 and 4 weeks showed that the 2 treatments were not statistically different in reducing key symptoms of reflux esophagitis (P > 0.05, Fisher’s exact test). Time for symptoms relief according to diary cards exhibited similar figures for both drugs using the Kaplan-Meier life tables.

**Predictive factors**

For both treatments, the healing rates after 4 weeks were lower in grade III than in grade II esophagitis (69 vs 89%, per-protocol analysis, P = 0.0001), with no grade-dependent significant difference between groups. Healing rates in subgroups of patients classified according to gender, age, weight, smoking behavior and previous relapses of reflux esophagitis did not reveal differences neither between treatment nor between the analyzed subgroups.

Symptoms at day 14 were substantially subsided in patients with mild to moderate symptoms at study entry versus those with severe symptoms (P = 0.0007). Symptom relief rates after 2 weeks were lower in stage III esophagitis than in stage II (64 vs 78%, per-protocol analysis, P = 0.02) (table III). Symptom relief rates in subgroups of patients classified according to gender, age, weight, smoking behavior and previous relapses of reflux esophagitis did not reveal differences neither between treatment nor between the analyzed subgroups.

**Safety**

Adverse events were reported by 63/225 (28%) patients in the pantoprazole group and by 39/236 (17%) patients in the lansoprazole group (ns). The relationship of the events with the study medication was considered to be “possible” in 33 cases for the pantoprazole group (15%) and 26 cases in the lansoprazole group (10%). Among those, 11 serious adverse events were reported. Nine were observed in the hospital population: 4 in the pantoprazole group (thrombophlebitis, intrahepatic cholestasis, alcohol intoxication and lower limb edema) and 5 in the lansoprazole group (dyspnea, epigastric pain, bradycardia, supraventricular tachycardia and traffic accidental death), respectively. Two were observed in the private practice population.

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**Table II.** Symptom relief during treatment (intention-to-treat and per-protocol population).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment group</th>
<th>Population</th>
<th>Patients free from symptoms, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intention-to-treat</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Total symptom relief</td>
<td>Pantoprazole</td>
<td>Intention-to-treat</td>
<td>173/226 (77)</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>Intention-to-treat</td>
<td>197/226 (87)</td>
</tr>
<tr>
<td>Heartburn relief</td>
<td>Pantoprazole</td>
<td>Intention-to-treat</td>
<td>194/226 (86)</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>Intention-to-treat</td>
<td>195/226 (86)</td>
</tr>
<tr>
<td>Acid regurgitation relief</td>
<td>Pantoprazole</td>
<td>Intention-to-treat</td>
<td>225/235 (96)</td>
</tr>
<tr>
<td>Pain on swallowing relief</td>
<td>Pantoprazole</td>
<td>Intention-to-treat</td>
<td>211/226 (93)</td>
</tr>
</tbody>
</table>
of 40 mg oral pantoprazole was assessed in patients with the treatment of acid-related disorders [1, 3]. The acid inhibitory potency was superior to the H2-receptor antagonist, ranitidine, in the treatment of esophagitis [1].

Discussion

The substituted benzimidazoles are very effective drugs for the treatment of reflux esophagitis and have been shown to be superior to the H2-receptor antagonist, ranitidine, in the treatment of acid-related disorders [1, 3]. The acid inhibitory potency of 40 mg oral pantoprazole was assessed in patients with duodenal ulcer using 24-h intragastric pH-metry. The mean of the 24-h median pH was 5.1 and the mean time period at which the pH was 3 or above was 20.1 h, and above 4 was 17.5 h [15]. In a recently published pH-metry comparison, lansoprazole 30 mg seemed to be slightly but significantly better than pantoprazole 40 mg [16].

Whether these putative differences in the pH-metry studies in healthy volunteers may have clinical implications for the management of patients suffering from reflux esophagitis had not been determined previously. Furthermore, the pharmacokinetics of lansoprazole are different in patients with esophagitis when compared to healthy volunteers [17]. In the present study, healing rates of 86% after 4 weeks in both treatment groups, and of 97% in the pantoprazole and 93% in the lansoprazole group after 8 weeks were observed in the per-protocol analysis. After 2 weeks treatment, more than three quarters of patients who had initially reported the key symptoms of heartburn, acid regurgitation or pain on swallowing were free from them in both treatment groups. After 4 weeks treatment, the percentage of patients free from these symptoms had increased to 86% in both groups. The differences in healing rates and symptom relief between the treatment groups were not statistically significant, suggesting that pantoprazole is comparable in efficacy to lansoprazole in the treatment of both the endoscopic and symptomatic manifestations of reflux esophagitis. Furthermore, the analysis of diary cards did not show any difference between lansoprazole and pantoprazole in the speed of symptom relief during the first 2 weeks, using a day-by-day assessment with the Kaplan-Meier life tables. More recently, Pilotto et al. [18, 19] have presented results on the treatment of elderly patients with esophagitis which confirmed the similar clinical efficacy of pantoprazole 40 mg and lansoprazole 30 mg once daily to cure esophagitis and relieve reflux symptoms.

In the present study, patients with grade III esophagitis did not respond as well as those with grade II esophagitis after 4 weeks. However, after 8 weeks the healing rates were very similar, indicating that PPIs are highly effective in more severe cases of esophagitis but that a longer course of treatment may be required as previously stated [1, 3, 20, 21].

Both drugs were equally well tolerated, with only 8-12% of patients in each treatment group reporting adverse events that are considered to have a possible relationship to the study medication. Serious adverse effects attributable to either drug were not recorded. Although there were some individual changes in laboratory values which may have been considered clinically significant, there were no apparent differences with respect to treatment groups.

Table IV. – Most frequent adverse events. 

<table>
<thead>
<tr>
<th>Event</th>
<th>Pantoprazole (n = 225)</th>
<th>Lansoprazole (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, n (%)</td>
<td>4 (1.8)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>3 (1.3)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>4 (1.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Skin disorders, n (%)</td>
<td>—</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Increase of ASAT/ALAT, n (%)</td>
<td>6 (2.7)</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

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REFERENCES


