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Acid suppression in healthy subjects following lansoprazole or pantoprazole

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SUMMARY

Aim: To compare the effect of lansoprazole, 30 mg once daily, with that of pantoprazole, 40 mg once daily, for the inhibition of gastric acid secretion.

Methods: Two randomized, single-blind, two-way, crossover studies were conducted in 74 healthy male volunteers. Lansoprazole, 30 mg, or pantoprazole, 40 mg, was administered once daily for five consecutive days with at least a 2-week washout period between regimens. Ambulatory 24-h intragastric pH was recorded at baseline and on days 1 and 5 of each crossover treatment period.

Results: On day 1 in both studies, lansoprazole, 30 mg, produced significantly higher mean 24-h intragastric pH values when compared to pantoprazole, 40 mg (3.78 vs. 3.08, $P < 0.001$, and 3.97 vs. 3.20, $P < 0.001$, in the first and second studies, respectively). In both studies, lansoprazole, 30 mg, produced significantly greater proportions of time that the intragastric pH was above 3, 4 and 5 when compared with pantoprazole, 40 mg ($P < 0.005$ in all comparisons). By treatment day 5 in the first study, lansoprazole, 30 mg, continued to produce a higher mean 24-h intragastric pH (4.15 vs. 3.91, $P = 0.014$) and a significantly greater percentage of time that the intragastric pH was above 4 (63% vs. 56%, $P = 0.017$) and 5 (41% vs. 30%, $P < 0.001$) when compared with pantoprazole, 40 mg. In the second study, the effects on intragastric pH were comparable between the two treatment groups. Headache was the most commonly reported adverse experience (nine lansoprazole-treated subjects, seven in the first study and two in the second study; six pantoprazole-treated subjects, five in the first study and one in the second study).

Conclusions: Lansoprazole, 30 mg once daily, produces a faster onset and greater degree of acid inhibition than pantoprazole, 40 mg once daily. The implications for these differences on symptom relief and healing of erosive oesophagitis should be explored.

INTRODUCTION

It is well established that proton pump inhibitors effectively suppress gastric acid secretion and are superior to histamine-2 receptor antagonists for treating patients with acid-related disorders. Healing of peptic ulcer disease and erosive oesophagitis and the relief of reflux symptoms are directly related to effective control of intragastric pH.[1–4] Comprehensive meta-analysis of 24-h intragastric pH data obtained from patients with peptic ulcer disease has confirmed the hypothesis that the healing of peptic ulcers and the relief of acid-related symptoms are significantly correlated with three key parameters. These are the degree and duration of acid suppression over

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the 24-h period and the duration of antisecretory treatment.[1–3]

The currently available proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are potent inhibitors of gastric acid secretion. However, the proton pump inhibitors differ with respect to several pharmacokinetic and pharmacodynamic properties, such as oral bioavailability, onset of acid inhibition and reduction of intragastric acidity. For example, the bioavailability of omeprazole, 20 mg, is approximately 35–40% after the first dose, but increases to approximately 65% after 5 days of continuous dosing.[5] In contrast, the relative bioavailability of lansoprazole, 30 mg, is higher, with a first-dose bioavailability between 80% and 90% which remains stable with continuous dosing.[6] The difference in bioavailability may explain the faster onset of acid suppression observed with lansoprazole, 30 mg, in comparative studies with omeprazole, 20 mg.[7, 8] A significantly greater proportion of lansoprazole-treated patients reported relief of reflux symptoms after 2 weeks when compared to omeprazole-treated patients in a meta-analysis of six comparative studies.[9]

The aim of these two crossover studies was to compare the acid inhibitory effects (as determined by 24-h intragastric pH monitoring) of lansoprazole, 30 mg once daily, with pantoprazole, 40 mg once daily, during 5 days of continuous administration in healthy volunteers.

SUBJECTS AND METHODS

Healthy male volunteers, 18–45 years of age, were eligible for participation in two, phase II, randomized, investigator-blind, two-way, crossover studies. Eligible subjects were required to be non-smokers, to weigh within 20% of the acceptable range of body weight according to the 1983 Metropolitan Life Tables for Height and Weight, and to have no evidence of a clinically significant medical condition. All subjects underwent a complete medical history and physical examination, with a panel of fasting laboratory evaluations, including serum gastrin and electrocardiogram. All subjects were required not to have used any prescription or over-the-counter medications within the preceding 2 weeks (i.e. antacids, aspirin, non-steroidal anti-inflammatory drugs or anti-ulcer medications); not to have received any investigational drug or participated in any other drug study within the previous month; not to have any history or evidence of drug or alcohol abuse; not to have donated blood products within the last month; and not to have any known allergies to either study medication. Each volunteer signed an informed consent form prior to participation in the study. The study protocol was approved by the investigational review board at each study site.

Following a screening period of up to 2 weeks prior to study initiation, eligible subjects were randomly assigned to one of two treatment groups. All subjects were treated with each of the two dosing regimens according to the sequence of their treatment group assignment. During each 5-day sequence, subjects were given lansoprazole, 30 mg once daily, or pantoprazole, 40 mg once daily. A washout period of at least 2 weeks separated the two dosing regimens. During each crossover period (from day 1 to the morning of day 6 of period 1, and from the evening of day 1 to day 6 of period 2), subjects were confined to the clinical investigation unit. Standardized meals were served at the same times and in the same sequence during the confinement phase of each crossover period. Xanthine-containing foods and beverages were prohibited during the study periods. Each dose of the study medications was administered orally 1 h before breakfast (08.00 h) with approximately 180 mL of water. The administration of medication was supervised and a thorough hand and mouth check was performed after each dose to ensure compliance with ingestion of the study medication.

Safety evaluations consisted of daily monitoring of vital signs, including sitting blood pressure, pulse and respiratory rates, oral temperature and weight. Samples for routine laboratory analyses were collected fasting prior to 08.00 h (before breakfast and before study medication dosing) on days 1 and 6 of each crossover period. Laboratory analyses included haematology, serum chemistry, urinalysis and serum gastrin. Following collection, gastrin specimens were immediately frozen and shipped to Covance Central Laboratory Services Inc., Indianapolis, IN, USA for analysis. Subjects were closely monitored for any adverse experiences and the investigator assessed each adverse experience for severity and possible relationship to the study drug. The severity of adverse experiences was defined as mild, moderate or severe, and the relationship of the event to study drug administration was categorized as definite, probable, possible or not related.

PHARMACODYNAMIC EVALUATION

Ambulatory 24-h intragastric pH monitoring was performed in all subjects at baseline (between 2 and 7 days prior to the first treatment dose of crossover period 1) and on days 1 and 5 of each of the crossover periods using an ambulatory pH recording system (Gastrograph Mark II, Medical Instruments Corporation, Switzerland at study centre 1 or a Digitrapper MD ambulatory pH monitoring unit, Medtronic Synectics, Shoreview, MN, USA at study centre 2). Subjects used the same recording unit at each evaluation. To permit the 24-h baseline and follow-up pH recordings to be made under controlled conditions, subjects were confined to the clinical investigation unit during the evaluations and consumed standardized meals.

The pH recording units were calibrated before and after each measurement using standard buffers (pH 1.0 and 7.0). The 24-h pH recordings began at approximately 08.00 h. A combination glass electrode incorporating both pH and reference electrodes (Ingold Messtechnik AG, Urdorf, Switzerland) was inserted through the nares to a distance of approximately 55 cm, and positioned in relation to the point of a significant drop in pH readings. Intragastric pH was recorded every 4 s during the 24-h period and the data stored for subsequent analysis.

PHARMACOKINETIC EVALUATION

Blood specimens for the determination of lansoprazole or pantoprazole kinetics were collected from each subject on days 1 and 5 of each crossover period at: 0 h (prior to 08.00 h dose) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 h after dosing. All blood samples were collected in heparinized tubes and immediately placed on ice. They were centrifuged at approximately 5 °C within 2 h of sampling. The plasma samples were collected immediately after centrifuging and frozen to a temperature of −20 °C until analysis (Harris Laboratories, Lincoln, NB, USA).

The pharmacokinetic parameters of lansoprazole and pantoprazole were obtained using non-compartmental pharmacokinetic methods. The maximum observed plasma concentration (C_{max}) and the time to the maximum observed concentration (T_{max}) were taken directly from the plasma concentration measurements. The area under the plasma concentration–time curve over the 24-h time interval (AUC_{24}) was calculated using the linear trapezoidal rule. The terminal elimination rate constant (β) was obtained from the slope of the least-squares linear regression fit of the logarithms of measurable concentrations vs. time in the log-linear terminal phase of the curve. The terminal half-life ($T_{1/2}$) was calculated as $\ln(2)/\beta$.

STATISTICAL ANALYSIS

The effect of each drug regimen on the 24-h intragastric pH was compared with a two-way crossover model that included the effects of site, sequence, the interaction of site and sequence, subject nested within site and sequence combination, regimen, period, the interaction of regimen and site and the interaction of period and site. A random effects model was used for the analysis of subject effect, while all other effects were analysed with a fixed model. Parametric analysis was performed on the mean 24-h intragastric pH, mean pH at post-dosing intervals of 0–5 h, 6–10 h, 11–15 h and 16–24 h, and the percentage of time that the intragastric pH was above the thresholds of 3, 4 and 5 during the 24-h recording period. Analysis of covariance was used to explore the relationship between the 24-h mean intragastric pH and the logarithm of the 24-h area under the concentration–time curve for lansoprazole and pantoprazole.

Statistical significance was considered when the P value was less than or equal to 0.05.

RESULTS

Thirty-eight healthy male volunteers with a mean age of 25 years (range, 18–39 years) and a mean 24-h intragastric pH at baseline of 2.52 were enrolled in the first study. One subject discontinued during the screening period and one subject completed only the lansoprazole treatment arm. A total of 36 healthy males with a mean age of 34 years (range, 21–45 years) and a mean 24-h intragastric pH of 2.26 at baseline enrolled in the second study. One subject discontinued the study prematurely and one subject completed only the lansoprazole treatment period.

On day 1 in both studies, lansoprazole, 30 mg, produced a significantly greater increase in the mean 24-h intragastric pH compared with pantoprazole, 40 mg (3.78 vs. 3.08 and 3.97 vs. 3.20 in the first and second studies, respectively; both results $P < 0.001$). In both studies, significantly higher mean

intragastric pH values at time intervals 0–5 h, 6–10 h and 11–15 h were observed on day 1 in subjects treated with lansoprazole, 30 mg, when compared with pantoprazole, 40 mg (Figure 1a,b, $P < 0.001$). On day 1 in both studies, lansoprazole, 30 mg, produced significantly higher percentages of time that the intragastric pH was above 3, 4 and 5 when compared with pantoprazole, 40 mg (Figure 2a,b). In study 1, the percentage of time over the 24-h period that the intragastric pH was above 3, 4 and 5 for lansoprazole, 30 mg, when compared with pantoprazole, 40 mg, was 61% vs. 47%, 47% vs. 32% and 28% vs. 17%, respectively ($P \leq 0.001$ for all comparisons). Similar results were observed in study 2. The percentage of time that the intragastric pH was above 3, 4 and 5 on day 1 with lansoprazole, 30 mg, when compared with pantoprazole, 40 mg, was 63% vs. 41% ($P < 0.001$), 50% vs. 31% ($P < 0.001$) and 34% vs. 22% ($P = 0.005$), respectively.

By treatment day 5, acid inhibition with the two drugs differed between the two studies (Figure 3a,b). In study 1, the mean 24-h intragastric pH on lansoprazole, 30 mg, was significantly higher than that on pantoprazole, 40 mg (4.15 vs. 3.91, $P = 0.014$). However, the effects of the two regimens on 24-h intragastric pH on day 5 were comparable in study 2 (4.46 on lansoprazole, 30 mg, vs. 4.29 on pantoprazole, 40 mg, $P = 0.392$). When comparison was made at different post-dosing intervals, lansoprazole, 30 mg, provided significantly higher mean intragastric pH values at 0–5 h than did pantoprazole, 40 mg, in both studies (4.53 vs. 4.04 in study 1, $P \leq 0.006$; and 4.81 vs. 4.25 in study 2, $P < 0.02$). Lansoprazole, 30 mg, also produced a significantly higher mean intragastric pH at post-dosing interval 6–10 h in study 1 than did pantoprazole, 40 mg (4.93 vs. 4.60, $P = 0.006$). As illustrated in Figure 4(a), the percentage of time that the intragastric pH was above 4 and 5 was significantly greater with lansoprazole, 30 mg, when compared with pantoprazole, 40 mg, in study 1 (63% vs. 56%, $P < 0.02$ and 41% vs. 30%, $P < 0.001$, respectively). In study 2, only numerical differences in the percentage of time that the intragastric pH was above 3, 4 and 5 were observed between the treatment groups (Figure 4b).

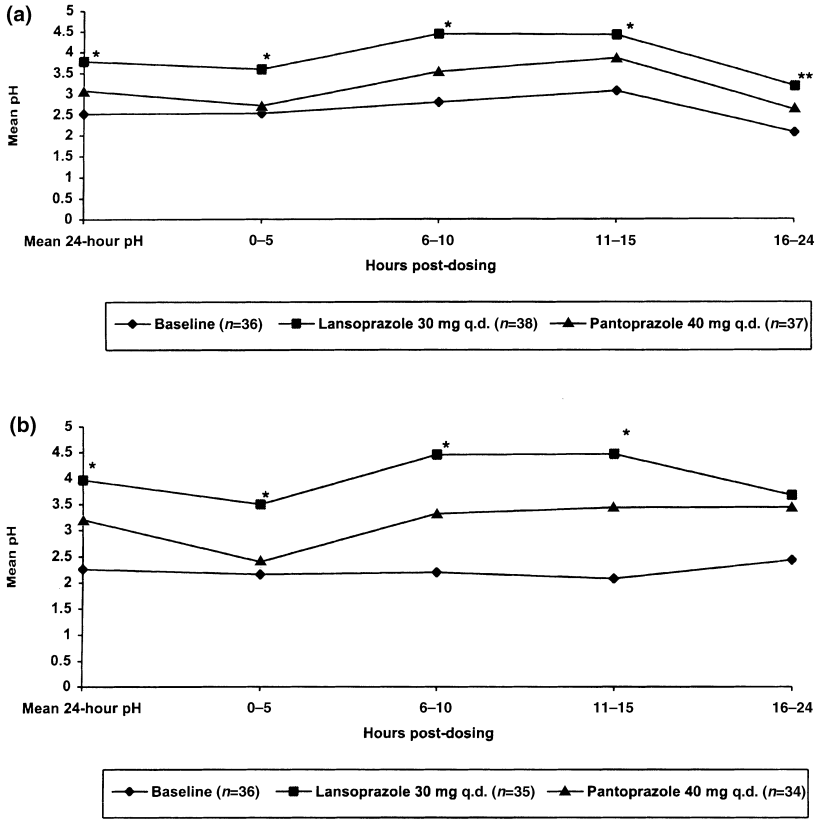

Figure 1. Mean intragastric pH at post-dosing time intervals on day 1 by treatment regimen (a, study 1; b, study 2).
*$P < 0.001$, lansoprazole vs. pantoprazole.
**$P = 0.01$, lansoprazole vs. pantoprazole.

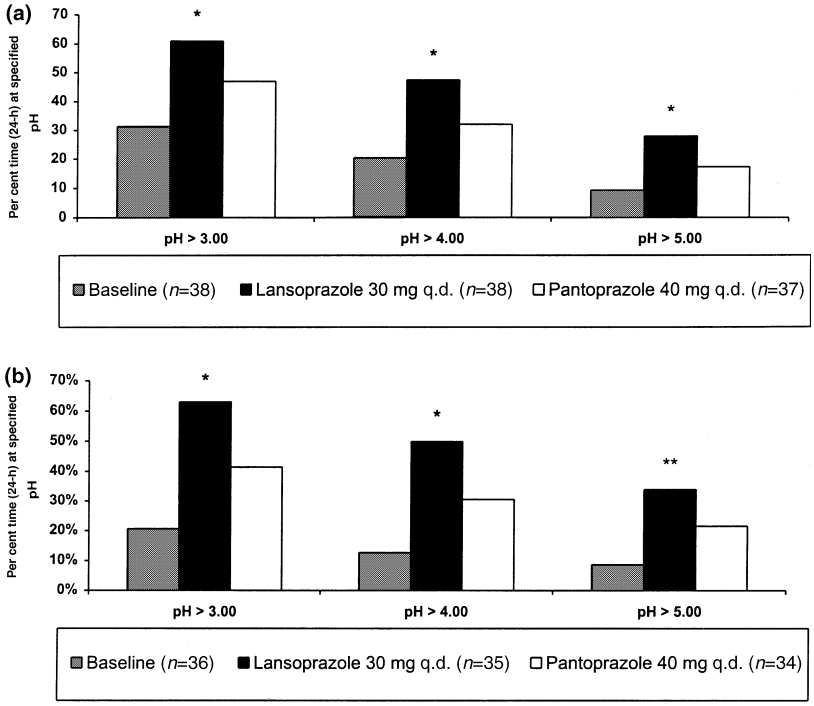

Figure 2. Mean percentage of time intragastric pH above 3, 4 and 5 on day 1 by treatment regimen (a, study 1; b, study 2). *$P < 0.001$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg. **$P = 0.005$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg.

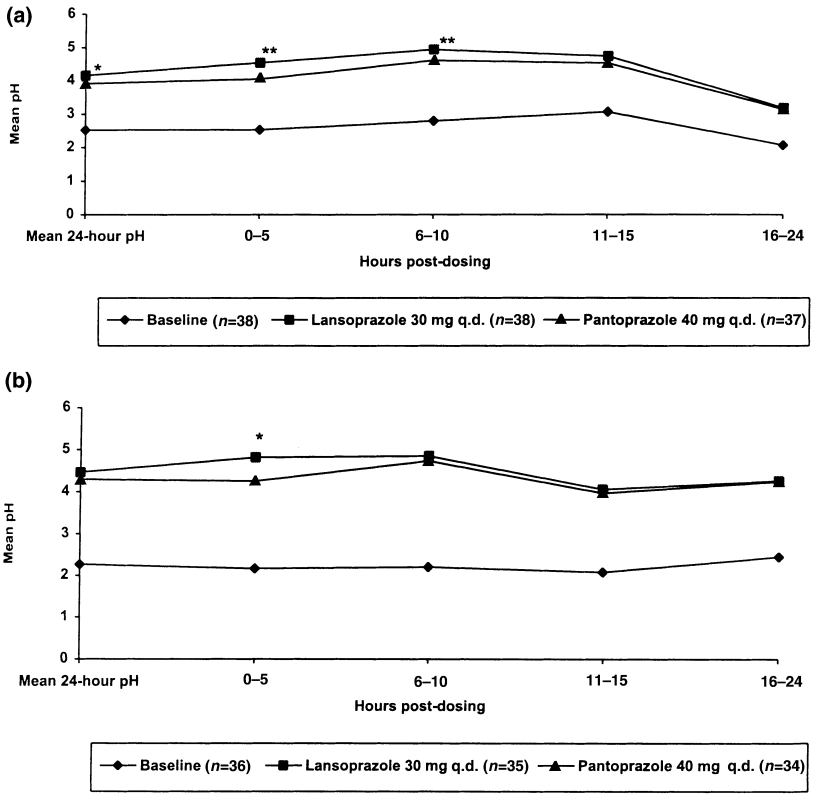

Figure 3. Mean intragastric pH at post-dosing time intervals on day 5 by treatment regimen (a, study 1; b, study 2). *$P < 0.02$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg. **$P \leq 0.006$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg.

No significant differences were observed when intragastric pH was analysed for sequence effect. On day 1, significant ($P \leq 0.05$) differences in period effect were observed between lansoprazole and pantoprazole in 24-h intragastric pH (both studies), pH above 3 (study 2 only), pH above 4 (both studies) and pH above 5 (study 1). In both studies, no significant differences in period effect were observed at day 5 or in site effect at either day 1 or day 5.

In both studies, the pharmacokinetic parameters of lansoprazole, 30 mg, observed on day 1 did not differ significantly from those observed on day 5 (Table 1). In contrast, while the pharmacokinetic parameters observed on day 1 and day 5 for pantoprazole, 40 mg, in the first study did not differ significantly, in the second study, the C_{max} and AUC_{24} values of pantoprazole were significantly greater on day 5 when compared to day 1 (Table 1). Figure 5 illustrates the plasma concentra-

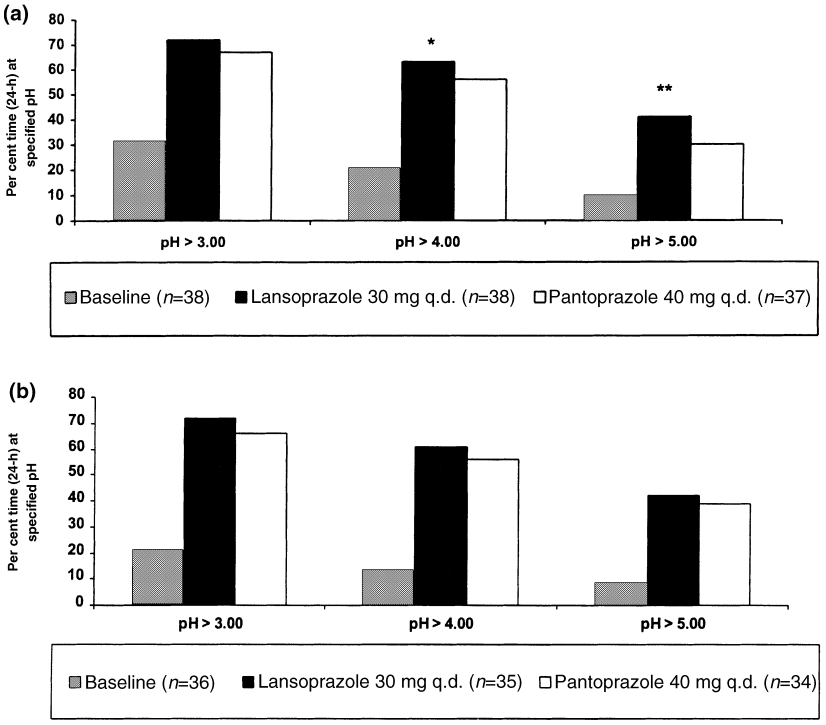

Figure 4. Mean percentage of time intragastric pH above 3, 4 and 5 on day 5 by treatment regimen (a, study 1; b, study 2). *$P < 0.02$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg. **$P < 0.001$, lansoprazole, 30 mg, vs. pantoprazole, 40 mg.

Table 1. Mean (± s.d.) pharmacokinetic parameters of lansoprazole and pantoprazole on days 1 and 5

	Lansoprazole, 30 mg/day†		Pantoprazole, 40 mg/day‡	
Parameter	Day 1	Day 5	Day 1	Day 5
Study 1				
C_{max} (ng/mL)	696 ± 274	703 ± 277	2074 ± 938	2121 ± 928
T_{max} (h)	1.3 ± 0.3	1.3 ± 0.4	2.3 ± 0.8	2.4 ± 1.1
AUC_{24} (ng.h/mL)	1419 ± 1025	1438 ± 1084	3266 ± 1847	3429 ± 2165
$T_{1/2}$ (h)	0.94 ± 0.29	0.95 ± 0.27	0.87 ± 0.25	0.87 ± 0.25
Study 2				
C_{max} (ng/mL)	850 ± 281	796 ± 323	2230 ± 1065	2757 ± 1288*
T_{max} (h)	1.5 ± 0.5	1.5 ± 0.4	2.5 ± 1.0	2.4 ± 1.2
AUC_{24} (ng.h/mL)	2536 ± 2042	2432 ± 2092	5906 ± 7107	7749 ± 10860*
$T_{1/2}$ (h)	1.20 ± 0.45	1.20 ± 0.43	1.15 ± 0.43	1.15 ± 0.42

*Statistically significantly different from day 1 value ($P \leq 0.05$).
†Study 1, $n = 37$; study 2, $n = 35$.
‡Study 1, $n = 36$; study 2, $n = 34$.

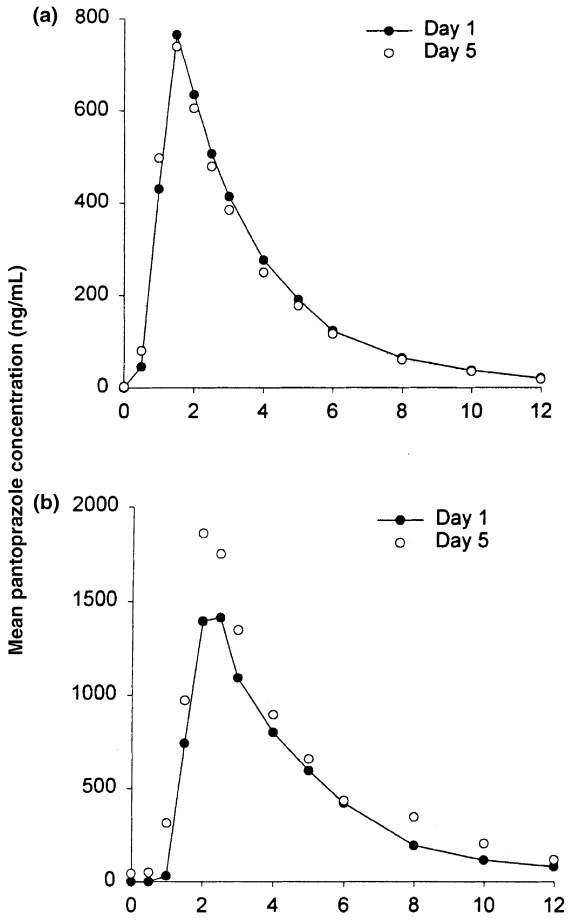

Figure 5. Mean plasma concentration–time profiles after 1 and 5 days of administration of: (a) lansoprazole, 30 mg once daily ($n = 35$); (b) pantoprazole, 40 mg once daily ($n = 34$) (study 2).

tion–time profiles of lansoprazole, 30 mg, and pantoprazole, 40 mg, in study 2.

Both treatment courses were well tolerated, with all reported adverse experiences being mild to moderate in severity. A total of 21 lansoprazole-treated subjects (13 of 38, 34% in study 1; and eight of 36, 22% in study 2) and 17 pantoprazole-treated subjects (nine of 37, 24% in study 1; and eight of 34, 24% in study 2) reported adverse events. Headache was the most frequently reported adverse experience in both studies. In study 1, headache occurred in seven subjects (18%) during lansoprazole treatment and five subjects (14%) during pantoprazole treatment. In study 2, headache occurred in two subjects (6%) during lansoprazole treatment and in one subject (3%) during pantoprazole treatment. No clinically significant differences in haematology, urinalysis or vital sign parameters were observed between the two dosing regimens in both studies. In study 1, clinically significant elevations in hepatic enzymes occurred in six subjects. Three of them occurred during or following pantoprazole treatment: one was considered to be related to the study drug and two were of unknown aetiology. Two subjects had elevations in hepatic enzymes following treatment with lansoprazole, and both were considered to be related to the study drug. Laboratory error was considered to be responsible for the elevated liver enzymes in one subject.

DISCUSSION

The onset of acid inhibition with antisecretory treatment is an important factor in the management of patients with acid-related disorders. Proton pump inhibitors with a high initial bioavailability may result in a more rapid onset of acid inhibition and faster relief of acid-related symptoms when compared with those with a slowly increasing bioavailability with repeated dosing.[10]

The results of these two studies performed in healthy male volunteers demonstrate that lansoprazole, 30 mg, has a significantly greater effect on acid secretion from the first dose, when compared with pantoprazole, 40 mg, with both drugs given in the morning. In both studies, the first dose of lansoprazole, 30 mg, resulted in a significantly higher mean 24-h intragastric pH and a significantly greater proportion of time that the intragastric pH was above 3, 4 and 5 when compared with pantoprazole, 40 mg. The superior effect of lansoprazole, 30 mg, over pantoprazole, 40 mg, on acid inhibition continued on day 5 in study 1. However, only numerical differences in acid suppression between the two treatment groups were observed on day 5 in study 2, although the trend was in favour of lansoprazole, 30 mg.

The results of this study confirm the pharmacokinetic and pharmacodynamic parameters of lansoprazole, 30 mg, as shown in other studies.[8, 11] The observed consistency of C_{max} and AUC_{24} between day 1 and day 5 with lansoprazole, 30 mg once daily, suggests that the maximal pharmacokinetic and pharmacodynamic effects were achieved after the first dose. In contrast, C_{max} and AUC_{24} for pantoprazole, 40 mg once daily, in both studies were greater on day 5 than on day 1, indicating that repeated dosing is necessary to achieve the maximal pharmacokinetic and pharmacodynamic effects.

The pharmacodynamic results of these two studies are consistent with those reported by Florent and Forestier, who found that lansoprazole, 30 mg, produced significantly higher mean 24-h intragastric pH values when compared with pantoprazole, 40 mg.[12] The effect of lansoprazole, 30 mg, on intragastric pH was maximal after the first dose (median percentage of time pH > 3 was 65% on day 1 and 61% on day 7) and remained constant throughout the 5-day treatment period. This is consistent with the report by Bell and Hunt.[11] However, the suppression of intragastric acidity between the first and last dose of pantoprazole increased significantly (median percentage of time intragastric pH > 3 was 35% on day 1 and 49% on day 7), suggesting that the bioavailability of pantoprazole, 40 mg, increased gradually with repeated dosing over time.

The effects on 24-h intragastric pH and the percentage of time that the intragastric pH was above 3 or 4, observed in the present study, are consistent with the findings of other comparative studies involving lansoprazole, 30 mg, omeprazole, 20 mg, and pantoprazole, 40 mg.[7, 8, 13–18] Several studies comparing the effects of lansoprazole, 30 mg, and omeprazole, 20 mg, on acid suppression have shown consistently that lansoprazole, 30 mg, achieves a greater percentage of time with an intragastric pH above 3[8, 13, 14] or 4[8, 13, 17, 18] when compared with omeprazole, 20 mg. In studies comparing the effects of proton pump inhibitors on meal-stimulated acid secretion, lansoprazole, 30 mg once daily, was significantly more effective than omeprazole, 20 mg once daily, for inhibiting meal-stimulated acid secretion, even on the first day of treatment.[19, 20] The more rapid onset of acid inhibition achieved with lansoprazole, 30 mg, than omeprazole, 20 mg, was confirmed in a recent study by Thoring *et al.*, who reported that, within 8 h of a single dose of lansoprazole, 30 mg, the mean intragastric pH was 2.9 compared with 2.0 following a single dose of omeprazole, 20 mg ($P = 0.005$).[7] An intragastric pH of greater than 4 was achieved approximately 2 h after taking lansoprazole compared to 4 h after omeprazole.[7]

There is some evidence to suggest that the more rapid onset of acid inhibition with lansoprazole, 30 mg, when compared to omeprazole, 20 mg, translates into a faster relief of acid-related symptoms. Mee *et al.* reported a statistically significant difference in the improvement in daytime heartburn between lansoprazole, 30 mg, and omeprazole, 20 mg, within 3 days of treatment ($P < 0.05$).[10] In another study of patients with erosive oesophagitis, Castell *et al.* confirmed that lansoprazole, 30 mg, was significantly more effective than omeprazole, 20 mg, in improving reflux-related symptoms within the first 2 weeks of treatment.[21] A recent meta-analysis by Huang *et al.* found that a significantly greater proportion of patients treated with lansoprazole, 30 mg, reported relief of reflux symptoms than those treated with omeprazole, 20 mg.[9]

Several investigators have found lansoprazole, 30 mg once daily, to be superior to omeprazole, 20 mg once daily,[7, 8, 13, 14, 17, 18] and pantoprazole, 40 mg once daily,[16] in raising intragastric pH. However, the difference in acid inhibition is less pronounced between omeprazole and pantoprazole. For example, Brunner *et al.* reported no significant differences in the mean 24-h intragastric pH, daytime and night-time intragastric pH and the duration of time that the intragastric pH was above 4 in a crossover study comparing pantoprazole, 40 mg once daily, with omeprazole, 40 mg once daily, for 7 days in 12 healthy volunteers.[22]

The highly predictable relationship between the degree and duration of intragastric pH control, specifically pH above 3 and 4, and the healing of acid-related disorders[1–4] explains why the proton pump inhibitors are significantly more effective than histamine-2 receptor antagonists for healing gastro-oesophageal reflux disease and controlling reflux symptoms.[3, 4, 23] A comprehensive and critical meta-analysis confirmed that the speed of healing of oesophagitis and the relief of heartburn achieved with the proton pump inhibitors are twice as fast as that with histamine-2 receptor antagonists.[4]

In conclusion, the findings of this study concur with previous reports that both lansoprazole, 30 mg once daily, and pantoprazole, 40 mg once daily, are highly effective in raising intragastric pH above the critical threshold of pH 4. Moreover, these results confirm that lansoprazole, 30 mg, produces a faster and stronger effect on intragastric acidity than pantoprazole, 40 mg. Given the results of this study, as well as others comparing omeprazole, lansoprazole and pantoprazole, the relative comparative potency on acid inhibition is lansoprazole, 30 mg > omeprazole, 20 mg = pantoprazole, 40 mg. Further studies are needed to determine whether the greater degree and faster onset of acid inhibition obtained with lansoprazole, 30 mg, compared to pantoprazole, 40 mg, translates into a more rapid relief of reflux symptoms and better cost-effectiveness.

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