

Control of intragastric pH with omeprazole 20 mg, omeprazole 40 mg and lansoprazole 30 mg

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SUMMARY

Background: Single daily doses of proton pump inhibitors, omeprazole and lansoprazole provide effective acid suppression and equal healing and symptom relief in patients with GERD. Despite this, controversy exists as to the efficacy of available proton pump inhibitors in the control of gastric acidity.

Aim: To assess the efficacy of omeprazole 20 mg vs. lansoprazole 30 mg and omeprazole 40 mg vs. lansoprazole 30 mg in intragastric pH control.

Methods: Study I: 12 *Helicobacter pylori*-negative volunteers (mean age 33 years) were treated with omeprazole 20 mg and lansoprazole 30 mg in random order before breakfast for 7 days. Study II: 24 subjects (mean age 36 years) were similarly treated with omeprazole 40 mg and lansoprazole 30 mg for 7 days after a baseline pH study. One week washout was allowed between studies. Subjects had the same meal on each study day. On day seven, a 24-h intragastric pH study

was performed. The percentage time for which gastric pH > 4 was analysed (Gastrosoft, Synectics Medical Inc.) and expressed as mean \pm s.d.

Results: (1) Omeprazole 20 mg and lansoprazole 30 mg showed no significant difference in the percentage time for which gastric pH > 4 in the daytime and night-time periods. (2) The percentage time for which pH > 4 with omeprazole 40 mg was significantly greater than lansoprazole 30 mg in both daytime ($61 \pm 19\%$ vs. $48 \pm 14\%$, $P < 0.001$), and night-time periods ($34 \pm 21\%$ vs. $26 \pm 14\%$, $P < 0.05$). (3) A large inter-subject variation existed in both studies. (4) In 10 subjects who participated in both studies, omeprazole 40 mg showed a significantly higher percentage time for which pH > 4 in the daytime ($69 \pm 18\%$ vs. $51 \pm 15\%$, $P = 0.015$) than omeprazole 20 mg.

Conclusion: These pH data support the therapeutic equivalency of FDA approved doses of omeprazole and lansoprazole.

INTRODUCTION

Omeprazole, the first proton pump inhibitor available, has now been used clinically for more than a decade. Since its introduction, it has raised the standard of therapy for acid-related disorders, particularly gastro-oesophageal reflux disease (GERD). Lansoprazole, the second proton pump inhibitor to come to market, has a

similar efficacy and safety profile to omeprazole. It is now recognized that proton pump inhibitors heal the great majority of patients with erosive oesophagitis (80–90%) and provide complete relief of heartburn for many GERD sufferers.^{1–4}

Published meta-analyses have demonstrated that efficacy in treating GERD is closely correlated with the acid inhibiting capacity of an agent, as measured by 24-h intragastric pH monitoring.⁵ The time spent with an intragastric pH of less than 3 or 4 has been identified as a good predictor of GERD-related symptoms and of the severity of oesophageal mucosal injury.⁶ In addition, it has been suggested that gastric acid break-

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through, predominantly at night and accompanying acid reflux, may explain why not all erosive oesophagitis patients heal during treatment with these drugs.⁷ Because healing rates and symptom relief are similar for omeprazole and lansoprazole at their recommended dose for healing of erosive oesophagitis (20 mg for omeprazole and 30 mg for lansoprazole), control of intragastric pH would be expected to be similar.^{8,9} However, there is some debate as to the relative efficacy of these drugs in control of intragastric pH.

This study was therefore performed to compare the relative abilities of omeprazole 20 mg and 40 mg, and lansoprazole 30 mg to raise intragastric pH above 3 and 4. Intragastric pH patterns during daytime and nighttime were studied separately.

SUBJECTS AND METHODS

Study design

The study was a two-way crossover therapeutic study in healthy volunteers and consisted of two separate trials. Volunteers were excluded if they had any unstable chronic disease, allergy to proton pump inhibitors, were taking NSAIDs or aspirin (> 325 mg/day), or were using any antisecretory therapy (including antacids, or prescription or over-the-counter H₂-RAs) on a regular basis. The protocol was approved by the Institutional Review Board, The Graduate Hospital, and a written informed consent was obtained from all subjects. All subjects were *Helicobacter pylori*-negative from serological testing before recruitment (FlexSure HP, SmithKline Diagnostics Inc., San Jose, CA).

In study I, omeprazole 20 mg in the morning (qAM) was compared with lansoprazole 30 mg qAM in 12 subjects (mean age 33 years old, range 24–48 years, two male and 10 female). In study II, omeprazole 40 mg qAM was compared with lansoprazole 30 mg qAM in 24 subjects (mean age 36 years old, range 24–54 years, four male and 20 female). In each study, the drug was administered openly but in random order, with an equal number of subjects treated first with omeprazole or

lansoprazole. Each subject was monitored via 24-h intragastric pH monitoring. A baseline 24-h pH study was performed on all subjects in study II. On day seven of each course of drug administration, a 24-h pH study was performed to evaluate the efficacy of gastric pH control. There was a 1-week washout period between the two drugs. The flow chart shows the sequence of drug administration and 24-h pH studies (Figure 1).

Ten subjects participated in both trials after a washout of at least 30 days. Their data were also used to compare the dose response of omeprazole 20 mg and 40 mg, and the reproducibility of lansoprazole 30 mg on 2 study days.

Study medication

Medication was given openly as capsules of omeprazole 20 mg, 40 mg (AstraZeneca Inc., Wilmington, Delaware, USA) or lansoprazole 30 mg (TAP Pharmaceuticals Inc., Deerfield, IL) 15 min before breakfast. The subjects were instructed to take their capsules with at least half a glass of water (75 mL). Compliance with medication was monitored via a diary.

Manometry

Manometric evaluation of the lower oesophageal sphincter was performed to place the pH probe with a 5-channel solid-state catheter (Konigsberg Inc., Pasadena, CA), using a station pull-through method. The pressure inversion point, just distal to the stable oesophageal baseline, defined the proximal border of the lower oesophageal sphincter.

Intragastric pH measurements

A 2.1 mm catheter (Synectics Inc., Minneapolis, MN) with a monocrystalline antimony electrode directed laterally 5 mm from the tip, and a separate skin reference electrode were calibrated prior to each recording as per the recommendations of the manufacturer. Calibration was conducted in buffers of pH 1.07 and

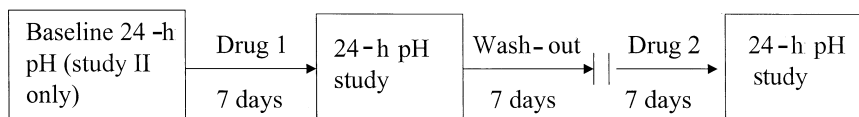


Figure 1. Flow diagram of the design of the two studies. Study drugs (omeprazole or lansoprazole) were given in random order; 24 h pH studies were conducted from 08.00 to 20.00 hours.

Table 1. The percentage time for which intragastric pH > 4 and >3 in study I

	Total		Daytime		Night-time	
	pH > 4	pH > 3	pH > 4	pH > 3	pH > 4	pH > 3
Omeprazole 20 mg	44.5 ± 15	50.8 ± 15	55.2 ± 19	64.4 ± 17	24.5 ± 17	30.5 ± 22
Lansoprazole 30 mg	47 ± 23	54.6 ± 22	58.9 ± 25	66.7 ± 23	26 ± 30	36.8 ± 29

Data presented as mean ± s.d.

7.01 at room temperature, and an adjustment for body temperature was introduced.

The pH probe was passed transnasally and swallowed with a minimal amount of water. It was then made to pass to the distal stomach, and retracted to the estimated position, with its tip 15 cm distal to the upper margin of the lower oesophageal sphincter. At this point, the catheter was located in the proximal stomach, about 5–7 cm distal to the cardia, in the fundic or upper body region. The sampling rate was 0.25 Hz and recorded data were stored in a multichannel solid-state data logger (Digitrapper Mark III, Synectics Inc.).

Recordings were started at 08.00 hours and lasted for 24 h. Subjects took meals at 08.00 hours, 12.00 hours and 18.00 hours, with a composition and calorie content they were accustomed to. These meals were repeated on each pH recording day. Each subject kept a diary in which he/she recorded the exact timing and composition of meals, and time spent in the recumbent position. The night-time period was defined as lasting from 22.00 hours until 06.00 hours, a period when the subject was asked to be recumbent.

At the end of the recording, data were edited in a dedicated software program (EsopHogram release 5.70,

Gastrosoft Inc., Irving, TX). The percentage time for which gastric pH > 4 and > 3 were calculated. Meal periods were excluded from analysis.

Statistical analysis

The percentage time for which intragastric pH > 4 and > 3 was analysed. Data were subjected to tests of normality and passed. Therefore parametric analysis was applied. Data are presented as mean ± s.d. The Student's *t*-test was used to compare the data of omeprazole 20 mg and lansoprazole 30 mg. One way ANOVA was used to compare the baseline, omeprazole 40 mg and lansoprazole 30 mg data. A paired *t*-test was used to compare the repeated studies for omeprazole 20 mg and 40 mg and lansoprazole 30 mg. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Study I: omeprazole 20 mg vs. lansoprazole 30 mg

The mean percentage time for which intragastric pH > 4 and > 3 was not significantly different between the two study groups. The total, daytime and night-time percentage times for which gastric pH > 4 with omep-

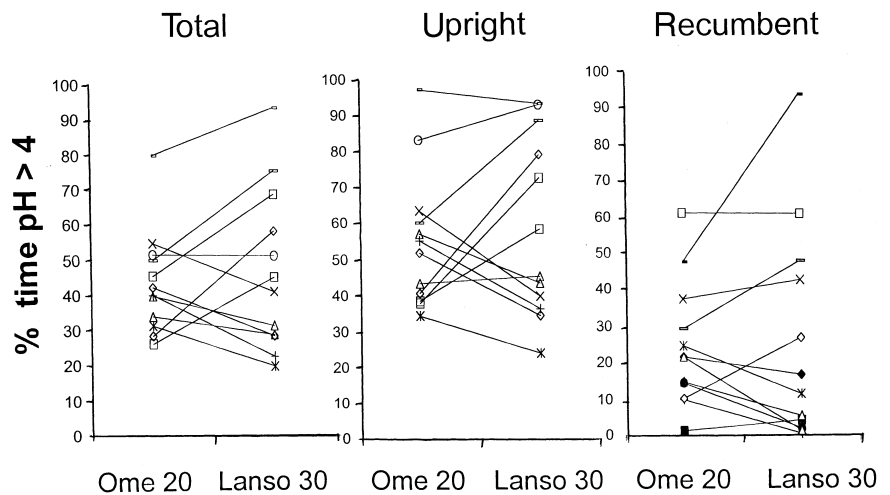


Figure 2. Individual data points for 12 subjects in study I, illustrating wide inter-subject variability with omeprazole and lansoprazole. Ome 20: omeprazole 20 mg; lanso 30: lansoprazole 30 mg.

razole 20 mg were $44.5 \pm 15\%$, $55.5 \pm 19\%$ and $24.5 \pm 17\%$, respectively, compared to times with lansoprazole 30 mg of $47.1 \pm 23\%$, $58.9 \pm 25\%$ and $26 \pm 30\%$, respectively (Table 1). A large inter-subject variation was noted in both groups (Figure 2). However, the coefficient of variation is smaller in the omeprazole group (34% in omeprazole and 49% in lansoprazole in total percentage time for which $\text{pH} > 4$) than in the lansoprazole group.

Study II: omeprazole 40 mg vs. lansoprazole 30 mg

Both omeprazole 40 mg and lansoprazole 30 mg showed significantly higher percentage times for which gastric $\text{pH} > 4$ and > 3 in the total, daytime and night-time periods compared to baseline. Omeprazole 40 mg was significantly superior to lansoprazole 30 mg in total and daytime times for which gastric $\text{pH} > 4$ and 3, and in the night-time time for which gastric $\text{pH} > 4$ (Table 2). Inter-subject variation was 30% in omeprazole 40 mg and 32% in lansoprazole 30 mg. Individual subject data are shown in Figure 3.

Dose response of omeprazole and reproducibility of lansoprazole

Ten subjects took part in both trials, taking omeprazole 20 mg, omeprazole 40 mg, and lansoprazole 30 mg on two separate occasions. There was a dose-dependent increase in the percentage time for which gastric $\text{pH} > 4$ and 3 in the total and daytime periods, but not the night-time period (Figure 4). Lansoprazole taken on two separate occasions did not show a difference in total ($44.7 \pm 19\%$ vs. $40 \pm 12\%$), daytime ($57.7 \pm 24\%$ vs. $51 \pm 12\%$) and night-time periods ($22.7 \pm 21\%$ vs. $24 \pm 16\%$), indicating a consistent response across studies.

DISCUSSION

Our data clearly demonstrate that treatment with omeprazole 20 mg o.d. and lansoprazole 30 mg o.d. in *H. pylori*-negative healthy subjects results in a similar intragastric pH during 24 h as well as during the daytime and night-time.

Table 2. The percentage time for which intragastric $\text{pH} > 4$ and > 3 in study II

	Total**		Daytime**		Night-time**	
	$\text{pH} > 4$	$\text{pH} > 3$	$\text{pH} > 4$	$\text{pH} > 3$	$\text{pH} > 4$	$\text{pH} > 3$
Baseline	8.6 ± 6	16.4 ± 8	11.7 ± 7	22.2 ± 9	3.3 ± 7	6.2 ± 9
Omeprazole 40 mg	$51.5 \pm 15^*$	$61.5 \pm 14^*$	$60.9 \pm 19^*$	$71.1 \pm 16^\ddagger$	$34.4 \pm 21^\ddagger$	40.7 ± 22
Lansoprazole 30 mg	39.5 ± 13	50.9 ± 12	47.7 ± 14	61.7 ± 14	26.3 ± 14	33.6 ± 15

Data presented as mean \pm s.d. Repeated measurement ANOVA and Neuman-Kuels post test used for comparison from baseline, omeprazole 40 mg and lansoprazole 30 mg for $\text{pH} > 4$ and > 3 .

** $P < 0.0001$; * $P < 0.001$ omeprazole vs. lansoprazole; $^\ddagger P < 0.001$ omeprazole vs. lansoprazole; $^\ddagger P < 0.05$ omeprazole vs. lansoprazole.

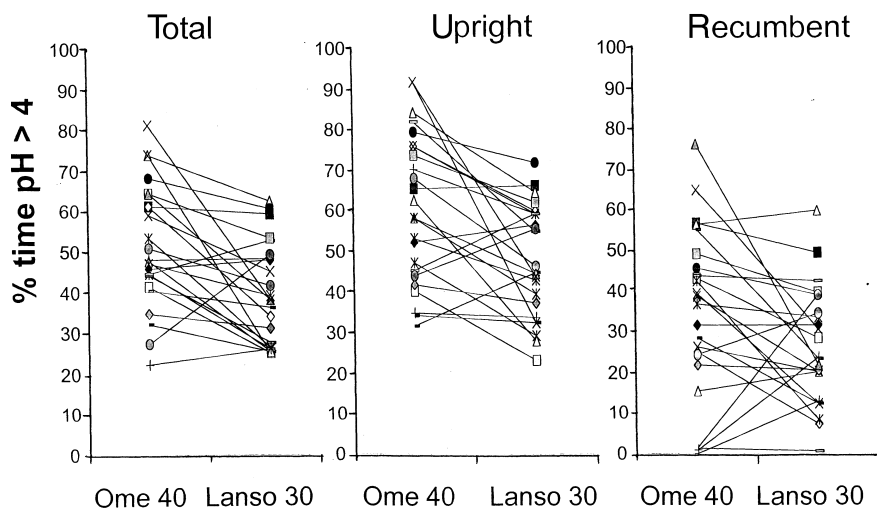


Figure 3. Individual data points for the 24 subjects in study II, showing inter-subject variability in percentage time for which $\text{pH} > 4$ with omeprazole and lansoprazole. Ome 40: omeprazole 40 mg; lanso 30: lansoprazole 30 mg.

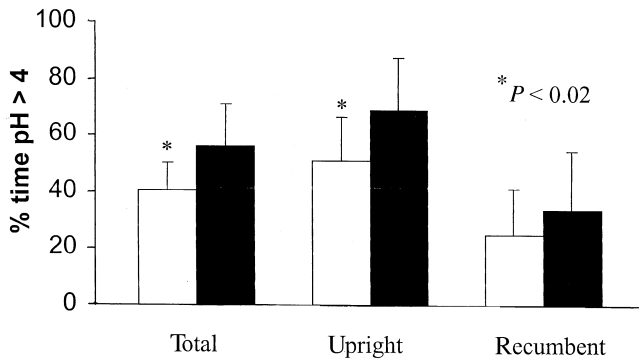


Figure 4. Bar graphs comparing percentage time for which pH > 4 in subjects who participated in both trials, indicating dose response for omeprazole at 20 and 40 mg doses. Open bars: omeprazole 20 mg; solid bars: omeprazole 40 mg. * $P < 0.02$ paired t -test.

Another published study in *H. pylori*-negative healthy subjects supports these findings. Geus *et al.* studied 16 healthy subjects (seven women and nine men) with a mean age of 27.9 years who were *H. pylori*-negative on serology testing.¹⁰ They found that there was no significant difference between treatment with omeprazole 20 mg o.d. and lansoprazole 30 mg when given once daily for 7 days. The investigators studied median intragastric pH as well as the time spent above pH thresholds 3, 4, and 5 for the 24-h period, during both daytime and night-time periods. Interestingly, when the dose of each drug increased to twice daily, omeprazole was significantly better than lansoprazole at suppressing night-time gastric acid.

Bruley Des Varannes *et al.* studied 12 healthy volunteers (mean age 25 years) with no prior history of peptic ulcer disease, without testing for *H. pylori*.¹¹ They administered omeprazole 20 mg o.d. or lansoprazole 30 mg o.d. for 7 days in a crossover manner and measured intragastric pH on day seven. They found that the effects of omeprazole and lansoprazole were similar. Only at one data point was lansoprazole 30 mg o.d. significantly better than omeprazole 20 mg o.d. This was the time spent with pH greater than 3 during the total 24-h period. Otherwise, there were no significant differences in the percentages of time spent above pH 1, 1.5, 2, 4, 5 and 6; there were also no significant differences in mean pH between the two drugs during either day or night.

Tolman *et al.* studied 14 healthy adult men (mean age 27 years), without testing for *H. pylori* infection.¹² In contrast to the aforementioned studies, they found that lansoprazole 30 mg o.d. for 5 days was significantly

better than omeprazole 20 mg o.d. in raising intragastric pH. The mean intragastric pH was higher, as was the time for which pH was above 3, 4, and 5. The lack of knowledge of *H. pylori* status in these subjects, however, confounds interpretation of these results, because response to proton pump inhibitor treatment is known to vary between infected and non-infected subjects.

In another similar study, where the *H. pylori* status of the subjects was unknown, Seensalu *et al.* studied 16 healthy volunteers (eight men and eight women) and found no significant difference in median pH or percentage of acid inhibition between two study groups taking either 20 mg omeprazole or 30 mg lansoprazole when observed on day five of therapy.¹³

Verdu *et al.* included only *H. pylori*-positive volunteers in their study of 18 subjects (11 men, seven women, aged 22–40 years).¹⁴ They found no differences between the median intragastric pH values obtained after seven days of treatment with 20 mg omeprazole or 30 mg lansoprazole. The lack of difference was demonstrated at pH 4 for the 24-h recordings of mealtime, night-time, or non-meal daytime values.

Janczewska *et al.* studied 10 patients with erosive oesophagitis and abnormal intra-oesophageal pH-monitoring, who were taking either omeprazole 20 mg o.d. or lansoprazole 30 mg o.d. for 5 days.¹⁵ They found that the median intragastric pH during daytime and night-time did not differ significantly between the two study groups.

In summary, the preponderance of published data supports the findings of the present study. There appears to be no major difference in intragastric pH achieved after treatment with omeprazole 20 mg or lansoprazole 30 mg. The lack of difference between the two proton pump inhibitors is reflected in the clinical setting in the results of healing studies in patients with erosive oesophagitis. Four major trials directly comparing the efficacy of omeprazole 20 mg and lansoprazole 30 mg in the healing of erosive oesophagitis have been published. All studies show similar efficacy of the two drugs.^{1–4}

Our study shows that omeprazole 40 mg is significantly better than both omeprazole 20 mg and lansoprazole 30 mg in raising intragastric pH to above 3 and 4. However, in clinical trials this moderate pharmacodynamic improvement has not resulted in significantly higher healing rates in most patients with erosive oesophagitis.

Mulder *et al.* compared the efficacy and safety of lansoprazole 30 mg q.d.s. and omeprazole 40 mg q.d.s. in 211 patients with erosive oesophagitis treated for 8 weeks. They found no significant difference in healing after either 4 weeks (87.5% vs. 80.6%) or 8 weeks (96.1% vs. 93.1%) of therapy with lansoprazole or omeprazole, respectively.¹⁶

Hetzel *et al.* compared omeprazole 20 mg with omeprazole 40 mg in 164 patients with erosive oesophagitis.¹⁷ After 8 weeks of treatment, they found no significant difference between the two treatment regimens with respect to healing (79% vs. 85%, respectively).

CONCLUSIONS

Our study supports data from the current literature, which demonstrates that there is no major difference with regard to intragastric pH and, as such, clinical outcome, when patients are treated with either omeprazole 20 mg daily or lansoprazole 30 mg daily. In normal subjects, omeprazole 40 mg daily provides an increase in intragastric pH that is statistically significantly higher than with lansoprazole 30 mg daily. The clinical importance of this difference is questionable.

ACKNOWLEDGEMENTS

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