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## Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms

Received: 14 April 2003 / Accepted: 27 May 2004 / Published online: 2 September 2004  
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**Abstract Objective:** To compare the effect of esomeprazole 40 mg with lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg on intragastric pH during single and repeated dosing in four separate studies in patients with symptoms of gastro-oesophageal reflux disorder (GERD).

**Methods:** In four randomised crossover studies, patients with symptoms of GERD received once-daily treatment with esomeprazole 40 mg or lansoprazole 30 mg (study A), omeprazole 20 mg (study B), pantoprazole 40 mg (study C) and rabeprazole 20 mg (study D) for 5 days. Continuous 24-h intragastric pH recording was performed on days 1 (except study B) and 5. Percentage of time over 24 h with intragastric pH greater than 4, 24-h median pH and the proportion of patients with pH greater than 4 for greater than or equal to 12 h and 16 h during the 24-h recording periods were investigated.

**Results:** In all four studies, esomeprazole 40 mg OD maintained intragastric pH greater than 4 for a significantly higher mean percentage of the 24-h period compared with all other proton pump inhibitors (PPIs) on days 1 (esomeprazole 40.6% versus lansoprazole 33.4%,  $P=0.0182$ ; esomeprazole 50.3% versus pantoprazole 29.1%,  $P<0.001$ ; esomeprazole 41.0% versus rabeprazole 29.4%,  $P=0.002$ ) and 5 (esomeprazole 57.7% versus lansoprazole 44.5%,  $P<0.0001$ ; esomeprazole 69.8% versus omeprazole 43.7%,  $P<0.0001$ ; esomeprazole 67.0% versus pantoprazole 44.8%,  $P<0.001$ ;

esomeprazole 59.4% versus rabeprazole 44.5%,  $P<0.0001$ ). Higher 24-h median pH and a higher proportion of patients with intragastric pH greater than 4 for greater than or equal to 12 h and 16 h were reported with esomeprazole 40 mg OD than with all the other PPIs in each study.

**Conclusion:** Esomeprazole 40 mg provides greater acid control in more patients and maintains intragastric pH greater than 4 for a longer period than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with symptoms of GERD.

### Introduction

Gastro-oesophageal reflux disease (GERD) is a common disorder that results from the abnormal and prolonged exposure of the lumen of the oesophagus to acidic gastric contents [1]. Prolonged acid exposure may cause symptoms such as heartburn and acid regurgitation and can lead to the development of mucosal injury of varying severity [2].

The severity of the disease correlates with the degree and duration of oesophageal acid exposure and is highly pH dependent [1, 2]. A threshold of intragastric pH 4 can be used to distinguish between aggressive and non-aggressive reflux [3]. Indeed, when the pH of the acid refluxate falls below 4, patients experience more intense symptoms and mucosal injury in the oesophagus [4].

Maintenance of intragastric pH above the threshold of 4 is, therefore, an important objective in the effective management of GERD. It is increasingly clear that the key to controlling symptoms and to healing oesophagitis is to decrease the duration of exposure of the oesophagus to the acidic gastric refluxate [4]. In fact, healing rates of erosive oesophagitis at 8 weeks by anti-secretory agents correlate directly with the ability to maintain an intragastric pH greater than 4 throughout

The experiments within this paper comply with the current laws of the countries in which they were conducted.

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most of each 24-h period [1, 4]. Moreover, effective and sustained acid control observed with proton pump inhibitor (PPI) treatment results in symptom resolution and high rates of oesophageal healing [5, 6]. Indeed, PPIs are currently recognised as the most effective treatment for GERD [7, 8].

Esomeprazole, the *S*-isomer of omeprazole, is subject to less first-pass hepatic metabolism than omeprazole and, therefore, has a higher systemic bioavailability [9]. This pharmacokinetic advantage with esomeprazole translates into more effective and sustained inhibition of 24-h intragastric pH compared with standard-dose (20 mg) and double-dose omeprazole [10, 11].

The four studies reported here compare the effect of esomeprazole 40 mg with lansoprazole 30 mg (study A) [12], omeprazole 20 mg (study B) [10], pantoprazole 40 mg (study C) [13] and rabeprazole 20 mg (study D) [14] on intragastric pH after a single dose and during repeated daily oral dosing in GERD patients.

The primary aim of each study was to compare the percentage of time with intragastric pH greater than 4 in the initial 4 h post-dose and over a 24-h period on day 1 (except for study B) and day 5 of each PPI treatment. Secondary study aims were to compare the 24-h median pH for each treatment and the proportion of patients with intragastric pH greater than 4 for at least 12 h and 16 h of each 24 h on day 1 (except for study B) and day 5 of each treatment period in each study.

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## Patients and methods

### Study design

All four studies were performed according to the ethics principles of the Declaration of Helsinki, and each protocol was approved by an independent ethics committee prior to study commencement. Written informed consent was obtained from all patients prior to inclusion into each study.

Patients (male and female, aged 20–60 years) who had experienced significant symptoms of GERD for at least 2 days per week for the 2 months prior to the study starting were enrolled into one of four, two-way ( $n=3$ ) or three-way ( $n=1$ ) crossover, randomised, single centre studies. The three-way cross-over study also included an esomeprazole 20 mg treatment arm, the results of which have already been published [10].

Patients were excluded if they had active peptic ulcer, a history of gastric surgery, abnormal motility disorders, symptoms indicating complications of GERD (e.g., melena, haematemesis) or severe allergic disease (studies A, C and D). In addition, patients using a PPI within 8 weeks prior to baseline or patients treated with anti-secretory or prokinetic drugs within 2 weeks prior to and during the study were excluded. Further exclusion criteria included pregnant or nursing women. Smokers were excluded in studies C and D but included in studies A and B.

A full medical history was taken, and a physical examination was performed at enrollment in addition to either a serological assessment (studies A, B and D) or a urea breath test (study C) to establish *Helicobacter pylori* status. Patients who were *H. pylori* positive were excluded from entering the studies (except study B, which included six *H. pylori*-positive patients). Any differences in sensitivity between the two tests for *H. pylori* were not likely to have an impact on the results, as comparisons were only made within each individual study and not between studies.

### Efficacy measurements

Eligible patients were randomised in each cross-over study to receive once-daily oral treatment with esomeprazole 40 mg and either lansoprazole 30 mg (study A), omeprazole 20 mg (study B), pantoprazole 40 mg (study C) or rabeprazole 20 mg (study D). Following an overnight fast, patients received PPI treatment each morning with a glass of water 30 min before breakfast at either the study centre on day 1 and day 2 (except for study B) and day 5 (under the supervision of the investigator) or at home. Medication was taken for 5 days, followed by a washout period of at least 13 days between each crossover treatment. On day 5 of each treatment period, treatment compliance was assessed by counting all unused medication. Rescue antacids were used in cases of severe reflux symptoms except during pH metry.

At the investigational site on day 1 (except for study B) and day 5, immediately after study drug administration, continuous 24-h intragastric pH recording was performed under standardised conditions using a micro electrode (Ingold M3 bipolar glass) attached to a data logger. The equipment used to record pH was a MMS Orion pH-data logger (Medical Measurement System, Netherlands) in studies A and D, a Digitrapper Mk III (Synectics AB Sweden) in study B and a Gastrograph Mk III (Medical Instruments Corporation, Solothurn, Switzerland) in study C. A two-point calibration of the electrode using standard buffers was made before and after each 24-h recording. The electrode was inserted intra-nasally and placed 8–10 cm below the oesophageal sphincter during pH recording. Each patient had an individual electrode throughout the study, and the electrode was placed in the same position during subsequent pH recordings. On study days, all meals were standardised during the day.

Routine laboratory safety variables were assessed before and at the end of the study (2–5 days after completion of the last treatment period). All adverse events were monitored throughout the study period and at the follow-up assessment. Clinically significant changes in laboratory variables and any recorded adverse events were followed up for as long as medically necessary.

## Statistical analysis

Percentage of time with intragastric pH greater than 4 during the 24-h period and at 4 h post first dose, as well as 24-h median pH on day 1 (except for study B) and day 5 were analysed using a mixed model analysis of variance, with fixed effects for period, sequence and treatment and a random effect for subject within sequence. The mean values of intragastric pH greater than 4 over the 24-h period and at 4 h post first dose for each treatment and the mean intragastric pH treatment differences were estimated with 95% confidence intervals (95% CI).

The area under the H<sup>+</sup> activity versus time curve was calculated by the software (MMS Database) in studies A and D. In studies B and C, the area was calculated after conversion of the pH values to H<sup>+</sup> activity (H<sup>+</sup> activity = 10<sup>-pH</sup>) using the trapezoid method. The mean values for each treatment and the mean treatment differences were estimated with 95% CI. The proportion of patients with pH greater than 4 for at least 12 h and 16 h during the 24-h period on day 1 (except for study B) and day 5 was also investigated. Significance was calculated using McNemar's test.

The studies were designed to enroll a maximum of patients (study A: 36, study B: 38, study C: 32, study D: 36) to have a set number of evaluable patients (study A: 32, study B: 36, study C: 28, study D: 32). Studies B and C were designed to show superiority assuming a true mean difference in percentage of time with intragastric pH greater than 4 of 20% and 11% points, respectively. Studies A and D were designed to estimate the mean difference in percentage time with intragastric pH greater than 4 with a 95% CI extending no more than 6.2% points and 9.3% points, respectively, from the observed mean difference.

## Results

A summary of baseline demographics and clinical characteristics of the study participants for each of the

four studies are presented in Table 1. Each of the four study populations were comparable between studies for gender, height and weight. In all studies, patients ranged in mean age from 27.5 years to 45.2 years. Patients who were found to be positive for *H. pylori* in pre-study tests were excluded from studies A, C and D, while the study population for study B included six *H. pylori*-positive patients. Any effects on intragastric pH caused by *H. pylori* infection should be balanced in both treatment periods due to the cross-over design used in each study.

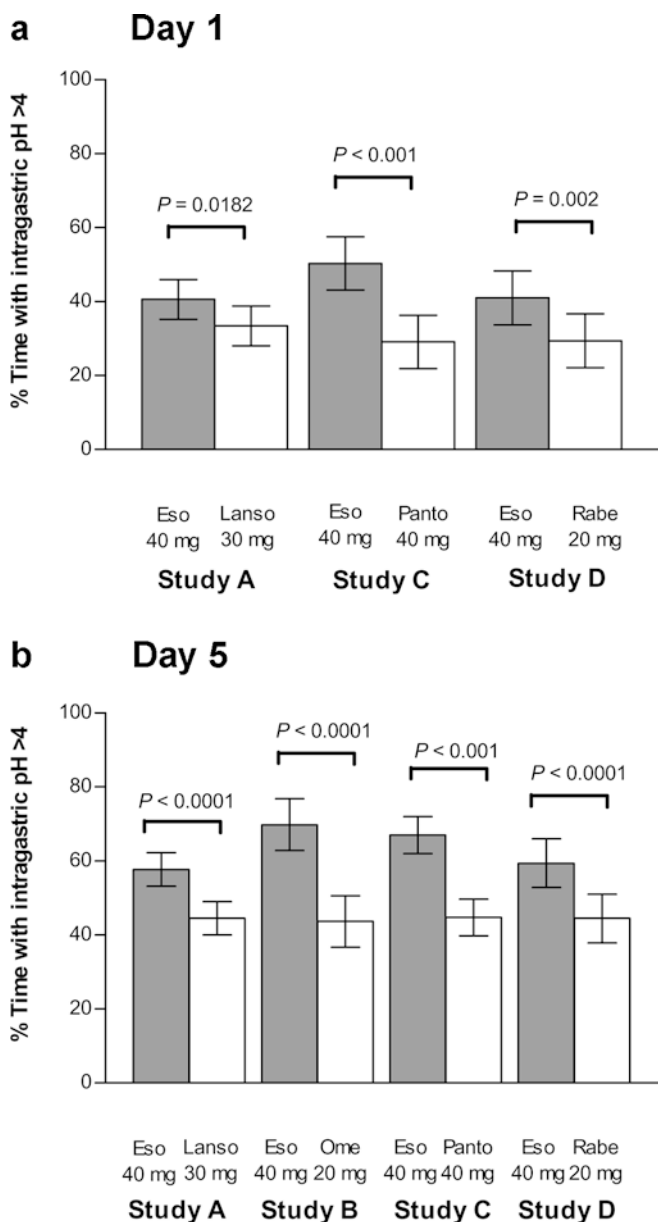
In total, 36 patients in study A, 38 patients in study B, 32 patients in study C and 35 patients in study D were randomised and received at least one dose of study medication. Due to technical failures in the pH data collection, a number of patients were excluded from the efficacy analyses in study A (day 1: *n*=6; day 5: *n*=5) and study D (day 1 and day 5: *n*=2). Two patients in each of studies B and C did not complete the studies. However, one patient in study C was included in the day 1 efficacy analysis. Therefore, the efficacy analysis on day 1 included 30 (study A), 31 (study B) and 33 (study C) patients. On day 5, the efficacy analysis included 31, 36, 30 and 33 patients in studies A, B, C and D, respectively. All patients who completed the study took the study drugs as directed.

In patients with symptoms of GERD, the mean percentage of time with intragastric pH greater than 4 on day 1 and day 5 in each study was significantly greater with esomeprazole 40 mg once daily than with all of the other PPIs (Fig. 1a, b). The mean differences between treatments in percentage time with intragastric pH greater than 4 during the 24-h period for esomeprazole 40 mg od compared with all other PPIs was significant in favour of esomeprazole in each study (Table 2). Esomeprazole 40 mg also provided significantly lower intragastric acidity than all the other PPIs after repeated administration (Table 3).

The number of hours with intragastric pH greater than 4 over the 24-h period on day 1 were: study A, esomeprazole 9.7 h versus lansoprazole 8.0 h; study C, esomeprazole 12.1 h versus pantoprazole 7.0 h; study D, esomeprazole 9.8 h versus rabeprazole 7.1 h.

**Table 1** Baseline demographics and clinical characteristics of the enrolled study populations in studies A–D. *Eso* esomeprazole, *Lanso* lansoprazole, *Ome* omeprazole, *Panto* pantoprazole, *Rabe* rabeprazole, *GERD* gastro-oesophageal reflux disease

Characteristics	Study A (Eso 40 mg versus Lanso 30 mg)	Study B (Eso 40 mg versus Ome 20 mg)	Study C (Eso 40 mg versus Panto 40 mg)	Study D (Eso 40 mg versus Rabe 20 mg)
Number of patients randomised	36	38	32	35
Gender (male:female)	17:19	16:22	13:19	14:21
Mean age (years)	31.3	45.3	27.9	30.5
Height (cm)	172.6	171	174.2	173.5
Weight (kg)	68.4	79.0	66.7	68.6
Duration of GERD, <i>n</i>				
< 1 Year	2	0	9	1
1–5 Years	16	10	15	14
> 5 Years	18	28	8	20
<i>Helicobacter pylori</i> status, <i>n</i>				
Negative	36	32	32	35
Positive	0	6	0	0



**Fig. 1a, b** Mean percentage of time with intragastric pH greater than 4 during the 24-h period on day 1 and (a) day 5 (b) after once-daily treatment with esomeprazole 40 mg versus lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg. Error bars denote 95% confidence intervals

On day 5, the number of hours with intragastric pH greater than 4 were: study A, esomeprazole 13.8 h versus lansoprazole 10.7 h; study B, esomeprazole 16.8 h versus omeprazole 10.5 h; study C, esomeprazole 16.1 h versus pantoprazole 10.8 h; study D, esomeprazole 14.3 h versus rabeprazole 10.7 h. Therefore, at steady state, intragastric pH remained above pH 4 in the 24-h treatment period between an average of 3.1 h and 6.3 h longer with esomeprazole 40 mg than the other PPIs tested.

In the first 4 h after study drug administration, esomeprazole initially provided significantly more time

with intragastric pH greater than 4 than pantoprazole (esomeprazole: 25% versus pantoprazole: 10.1%;  $P=0.001$ ) and rabeprazole (esomeprazole: 23.2% versus rabeprazole: 11.0%;  $P=0.006$ ) and showed a trend towards (not significant) increased acid control compared with lansoprazole (esomeprazole: 20.7% versus lansoprazole: 14.2%;  $P=0.186$ ). However, by the end of day 1, 24 h post first dose, the differences in intragastric acid control with esomeprazole compared with all the other PPIs in each study were significant in favour of esomeprazole.

In each of the four studies, the mean 24-h median intragastric pH was higher for esomeprazole compared with all the other PPIs on day 1 and day 5. In addition, the mean differences between all the PPI treatments for this variable were significant in favour of esomeprazole (Table 4). Esomeprazole was the only PPI to provide a median intragastric pH >4 at steady state and this was observed in all four studies. Furthermore, median intragastric pH profiles over the 24-h period on day 5 indicated that esomeprazole maintained a higher median pH than all the other PPIs throughout most of the daytime (Fig. 2a–d).

The proportion of patients with an intragastric pH maintained above 4 for greater than or equal to 12 h and 16 h on both day 1 and day 5 was higher following esomeprazole treatment than with each of the other PPIs for each study (Fig. 3a, b).

The safety and tolerability profile was similar for all PPIs studied. Almost all adverse effects were of mild to moderate intensity; headache, flatulence and diarrhoea were the most common adverse events in each of the studies. Laboratory test profiles were similar among the treatment groups in all studies, and no clinically relevant changes were observed.

## Discussion

In the four studies described here, the percentage of the 24-h period for which intragastric pH remained greater than 4 was significantly higher after single and repeated dosing with esomeprazole 40 mg than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg or rabeprazole 20 mg in GERD patients. In addition, in each study, esomeprazole maintained intragastric pH greater than 4 for at least 12 h or 16 h in more patients and achieved a higher median intragastric pH throughout the entire 24-h period. In all four studies, repeated doses of all PPIs were well tolerated.

These results are consistent with those from previous studies investigating the effect of esomeprazole versus other PPIs on intragastric pH in healthy volunteers. In these studies, esomeprazole also maintained intragastric pH greater than 4 for a higher percentage of time over the 24-h period than lansoprazole or rabeprazole (esomeprazole 65% versus lansoprazole 53%; esomeprazole 61% versus rabeprazole 45%). Additionally, the proportion of subjects with intragastric pH greater than

**Table 2** Mean differences in time with intragastric pH greater than 4 during the 24-h period on day 1 and day 5 after once-daily treatment with esomeprazole 40 mg versus lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg.

*Eso* esomeprazole, *Lanso* lansoprazole; *Ome* omeprazole, *Panto* pantoprazole, *Rabe* Rabeprazole, *GERD* gastro-oesophageal reflux disease, *CI* confidence interval

Results of four separate studies in evaluable GERD patients	Mean difference in percent of 24 h period with pH > 4 (95% CI)	P value
Day 1		
Eso 40 mg versus Lanso 30 mg (study A)	7.2 (1.3–13.0)	0.0182
Eso 40 mg versus Panto 40 mg (study C)	21.2 (15.0–27.4)	<0.001
Eso 40 mg versus Rabe 20 mg (study D)	11.6 (4.5–18.7)	0.002
Day 5		
Eso 40 mg versus Lanso 30 mg (study A)	13.2 (8.9–17.4)	<0.0001
Eso 40 mg versus Ome 20 mg (study B)	26.1 (19.8–32.4)	<0.0001
Eso 40 mg versus Panto 40 mg (study C)	22.2 (18.6–25.7)	<0.001
Eso 40 mg versus Rabe 20 mg (study D)	14.8 (8.1–21.6)	<0.0001

**Table 3** Mean area under H<sup>+</sup> activity versus time curve (mmol\*h/l) after repeated administration (day 5) of esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with symptoms of GERD. *Eso*

esomeprazole 40 mg, *Lanso* lansoprazole 30 mg, *Ome* omeprazole 20 mg, *Panto* pantoprazole 40 mg, *Rabe* rabeprazole 20 mg, *GERD* gastro-oesophageal reflux disease, *CI* confidence interval

	Mean area under H <sup>+</sup> activity versus time curve (95% CI)	Mean difference (95% CI)	P value	
Study A (n=31)	Eso 119.9 (82.3–157.5)	Lanso 196.0 (157.8–234.2)	–76.1 (–112.3 to –39.9)	0.0002
Study B (n=36)	Eso 61.3 (39.3–83.3)	Ome 210.8 (148.0–273.6)	–149.5 (–209.9 to –89.1)	<0.0001
Study C (n=30)	Eso 77.3 (51.2–103.5)	Panto 173.0 (134.0–212.1)	–95.7 (–132.2 to –59.1)	<0.0001
Study D (n=33)	Eso 144.4 (106.0–182.8)	Rabe 294.4 (205.1–383.8)	–150.0 (–235.8 to –64.3)	0.0012

**Table 4** Mean 24-h median intragastric pH after 5 days' once-daily treatment with esomeprazole 40 mg vs lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with symptoms of GERD

	Mean 24-h median intragastric pH on day 5 (SD)	Mean difference (SD)	
Day 1			
Study A (n=30)	Eso 40 mg: 3.5 (0.9)	Lanso 30 mg: 3.2 (0.6)	0.3 (0.9)
Study C (n=31)	Eso 40 mg: 3.9 (1.2)	Panto 40 mg: 2.9 (0.9)	1.0 (0.9)
Study D (n=33)	Eso 40 mg: 3.4 (1.2)	Rabe 20 mg: 2.7 (1.0)	0.6 (1.0)
Day 5			
Study A (n=31)	Eso 40 mg: 4.3 (0.5)	Lanso 30 mg: 3.8 (0.5)	0.5 (0.5)
Study B (n=36)	Eso 40 mg: 4.9 (0.8)	Ome 20 mg: 3.6 (1.2)	1.3 (1.0)
Study C (n=30)	Eso 40 mg: 4.7 (0.7)	Panto 40 mg: 3.7 (0.6)	1.0 (0.6)
Study D (n=33)	Eso 40 mg: 4.4 (0.9)	Rabe 20 mg: 3.5 (1.0)	0.9 (1.2)

Eso = Esomeprazole; Lanso = Lansoprazole; Ome = Omeprazole; Panto = Pantoprazole; Rabe = Rabeprazole; GERD = gastro-oesophageal reflux disease; SD = standard deviation

4 for greater than or equal to 12 h and 16 h was higher after esomeprazole treatment than with lansoprazole and rabeprazole [15, 16].

Esomeprazole 40 mg has also been compared on a milligram basis with twice the standard dose of omeprazole (40 mg) in patients with symptoms of GERD in an open label crossover study. Esomeprazole 40 mg provided significantly more intragastric acid control than omeprazole 40 mg over the 24-h period on day 1 (48.6 versus 40.6%) and day 5 (68.4 versus 62.0%) [11]. Furthermore, esomeprazole 40 mg has recently been compared in a dose-ranging study with standard (30 mg) and double-dose lansoprazole 60 mg [17]. This study

showed that esomeprazole 40 mg provided significantly more time with intragastric pH greater than 4 than both lansoprazole 30 mg (61.3 versus 45.8%) and lansoprazole 60 mg (61.3 versus 51.7%) over the 24-h period at steady state.

These present studies reflect the results of previous pH-monitoring studies, which show standard-dose PPI treatment increases the median 24-h pH to varying degrees in GERD patients and healthy volunteers [18–20]. However, a higher median pH was recorded in some studies with the other PPIs than was recorded in the present studies. Although a similar randomised, double-blind, cross-over design was used in all studies,

**Fig. 2** Comparative median intragastric pH profiles over the 24-h period on day 5 of once-daily treatment with (a) esomeprazole 40 mg vs lansoprazole 30 mg, (b) esomeprazole 40 mg vs omeprazole 20 mg, (c) esomeprazole 40 mg vs pantoprazole 40 mg, and (d) esomeprazole 40 mg vs rabeprazole 20 mg

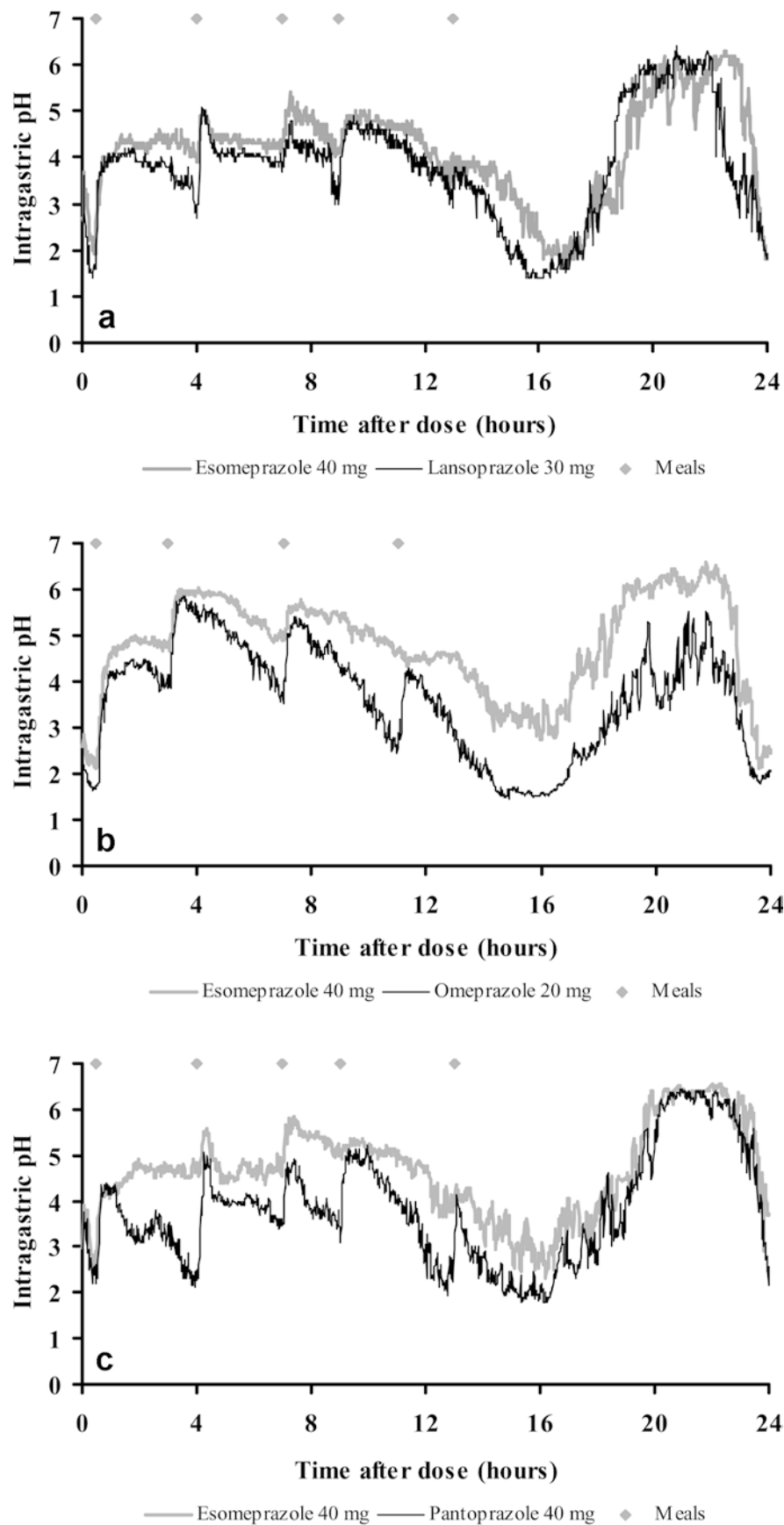


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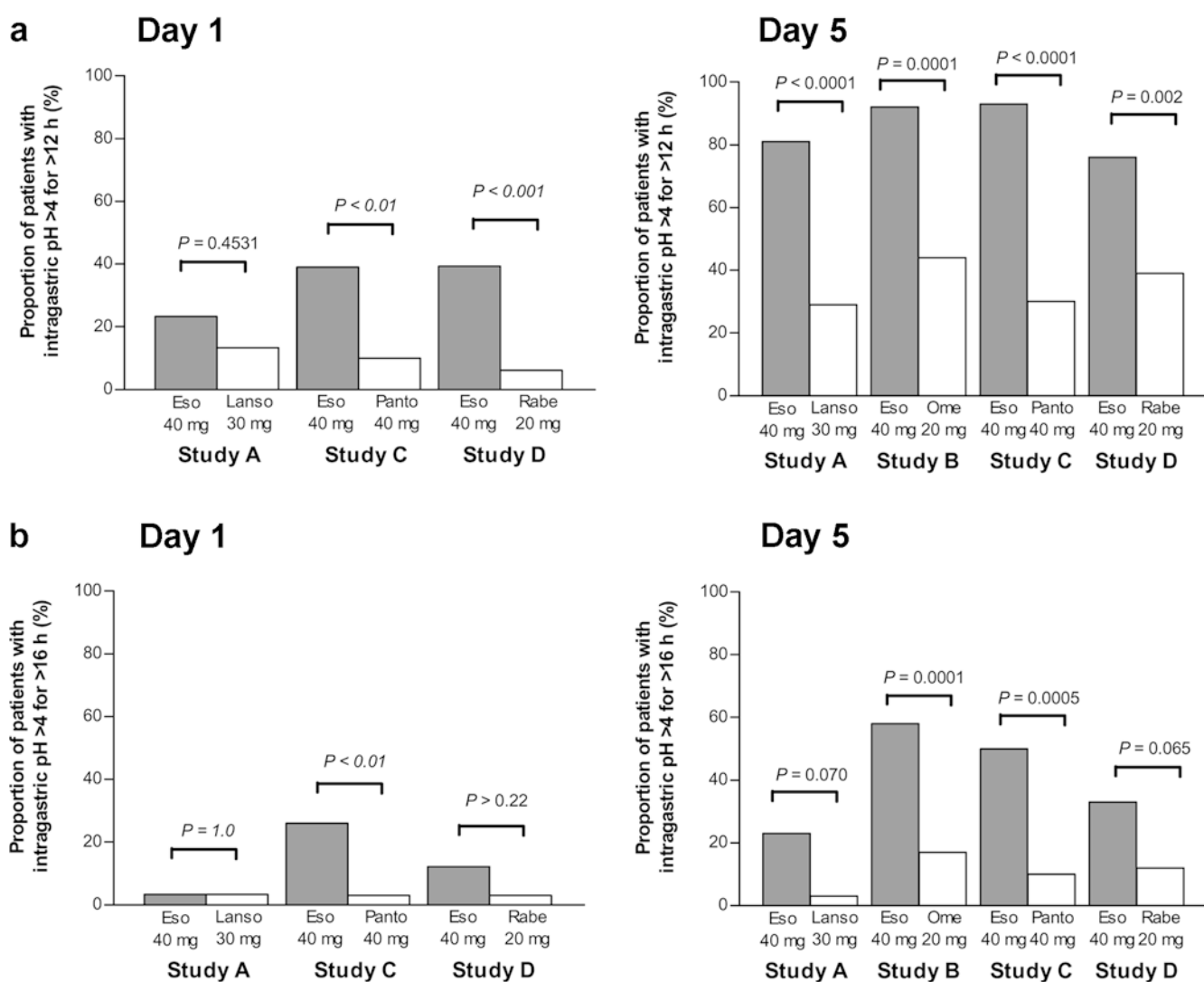
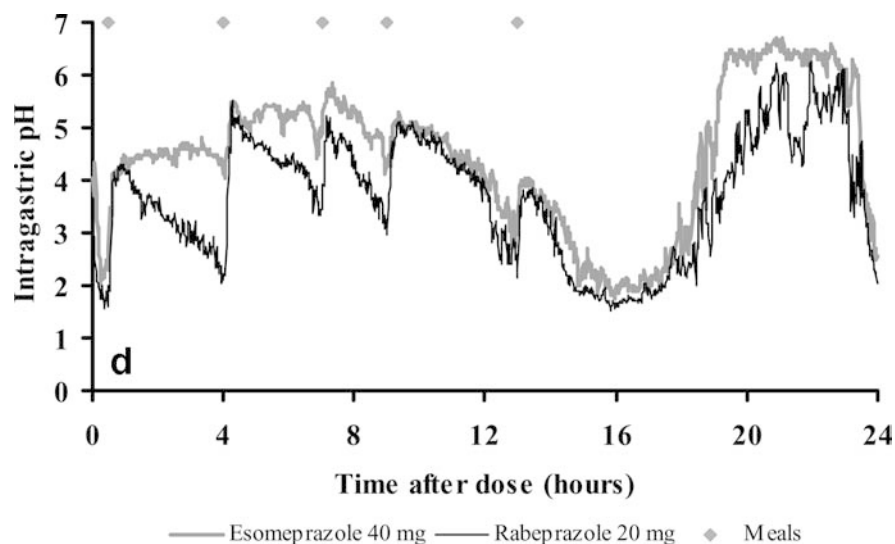


Fig. 3a, b Proportion of patients with intra-gastric pH greater than 4 for greater than or equal to 12 h (a) and 16 h (b) on day 1 and day 5 after once-daily treatment with esomeprazole 40 mg versus lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg

treatment periods and washout periods were variable. In addition, different methodologies used for measuring intragastric pH, different standardised food regimens on the pH measurement day (timing and the buffering qualities of different foods) and differing patient populations (severity of GERD at baseline, *H. pylori* status, age and smoking habits) make it difficult for direct comparisons to be made between individual studies of differing designs. In these present studies, different data loggers were used in each study. However, it has been previously demonstrated that when a pH glass electrode was attached to two different data loggers simultaneously in the same subject during a 24-h pH recording, no significant differences in pH values were detected (Daniel Schindler, personal communication).

A direct relationship between the degree and duration of acid reflux and the extent of mucosal injury is observed in GERD [21]. In fact, the rate of healing of oesophagitis correlates directly with the duration for which intragastric pH greater than 4 over a 24-h period [4, 21, 22]. In these present studies, esomeprazole was the only PPI to achieve a median 24-h pH greater than 4 at steady state, therefore consistently providing a median pH higher than that associated with mucosal healing in all four studies. Furthermore, a higher median pH was observed with esomeprazole than all of the other PPIs throughout the waking hours, which is the most important period to control acid in GERD patients. The greater acid control shown in each of these studies with esomeprazole 40 mg may, therefore, translate into more effective symptom resolution and mucosal healing. Indeed, in comparative studies with omeprazole and lansoprazole in GERD patients, esomeprazole provided significantly greater healing of erosive oesophagitis [23–25]. Furthermore, esomeprazole 20 mg has provided significantly higher remission rates than lansoprazole 15 mg following 6 months maintenance therapy in patients with healed reflux oesophagitis [26]. These clinical advantages reported for esomeprazole may also extend to comparison with other PPIs, such as pantoprazole and rabeprazole; however, further studies are required.

In conclusion, we have shown in four separate studies that esomeprazole 40 mg maintains significantly greater acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with symptoms of GERD.

**Acknowledgements** This study was supported by a grant from AstraZeneca R&D Mölndal, Mölndal, Sweden.

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