Aliment Pharmacol Ther 1998; 12: 1079–1089.

A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects

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Accepted for publication 30 June 1998

SUMMARY

Background: Rabeprazole (LY307640, E3810) is a new, potent, proton pump inhibitor. A single daily 20 mg dose significantly decreases 24-h intragastric acidity. There are no data currently available directly comparing the effect of rabeprazole on 24-h acidity with established proton pump inhibitors.

Aim: To compare the effects of rabeprazole 20 mg o.m. and omeprazole 20 mg o.m. on 24-h intragastric acidity and plasma gastrin concentration in a randomized, double-blind, placebo-controlled trial, in healthy *H. pylori*-negative subjects.

Methods: Twenty-four healthy male volunteers, negative for *H. pylori* infection by serology and ^{13}C-urea breath test, were studied on the 1st and 8th day of dosing with either placebo, rabeprazole 20 mg or omeprazole 20 mg, once each morning, in a crossover fashion. On days 1 and 8, hourly intragastric acidity was measured by gastric aspiration for 24 h from 08.00 hours. On day 8, plasma gastrin concentrations were also measured hourly from 08.00 to 24.00 hours, then every 2 h thereafter.

Results: A single dose of both rabeprazole and omeprazole significantly decreased 24-h intragastric acidity compared with placebo. The 24-h acidity on day 1 was significantly decreased for rabeprazole compared with omeprazole (331 vs. 640 mmol.h/L, $P < 0.001$), resulting in a significantly higher median 24-h intragastric pH and longer times at which intragastric pH was > 3 and > 4. On day 8 of dosing, the decrease in 24-h intragastric acidity was greater with rabeprazole than with omeprazole, but the difference was not statistically significant (160 vs. 218 mmol.h/L, $P = 0.1$). However, 24-h plasma gastrin concentration (1687 vs. 1085 pmol.h/L, $P < 0.01$) and percentage time that intragastric pH was > 3 (69 vs. 59%, $P = 0.008$) and > 4 (60 vs. 51%, $P = 0.03$) were significantly greater.

Conclusions: Rabeprazole 20 mg once daily has a significantly faster onset of antisecretory activity than omeprazole 20 mg once daily. After 8 days the differences in intragastric pH > 3 and > 4 holding times persisted, but there was no significant difference in 24-h acidity.

INTRODUCTION

Rabeprazole (E3810, LY307640) is a new proton pump inhibitor. Like other proton pump inhibitors, it is a substituted benzimidazole which non-competitively inhibits parietal cell H^+,K^+-ATPase.[1] Initial *in vitro* and *in vivo* studies have demonstrated that rabeprazole is a potent inhibitor of gastric acid secretion[2, 3] and is effective at healing peptic ulceration.[4] Subsequent clinical studies have confirmed rabeprazole's potent antisecretory activity[5–7] and efficacy in the treatment of both peptic ulcer disease and gastro-oesophageal reflux disease (GERD).[8–10]

Omeprazole was the first proton pump inhibitor to be marketed and is the most extensively studied. Clinical trials with omeprazole have established the role of this

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class of drugs in the treatment of peptic ulcer disease, Zollinger–Ellison Syndrome, GERD and cure of *Helicobacter pylori* infection.[11, 12] A recent series of studies examining the effect of *H. pylori* infection on the antisecretory activity of omeprazole has shown that the presence of *H. pylori* infection significantly enhances the effect of omeprazole on 24-h intragastric pH.[13–15] This may explain, in part, the variability in antisecretory activity of omeprazole seen in otherwise healthy volunteers, and the greater antisecretory activity seen in studies involving peptic ulcer patients compared with those involving healthy volunteers.[16] It also makes it essential that *H. pylori* status is taken into account in all future studies assessing the antisecretory activity of proton pump inhibitors.

Comparative *in vitro* and ulcer model studies have shown rabeprazole to be equally if not more potent than omeprazole in inhibiting H^+,K^+-ATPase and acid secretion, and in healing ulcers.[2–4] There are no human data directly comparing the relative antisecretory activities of rabeprazole and omeprazole, although multicentre, randomized, double-blind clinical studies, comparing rabeprazole 20 mg once daily and omeprazole 20 mg once daily for 4–8 weeks, have shown equivalent healing rates for duodenal ulcers, gastric ulcers and erosive oesophagitis.[17–19]

The aim of the present study was to compare the effects of single and repeat dosing with rabeprazole 20 mg o.m. and omeprazole 20 mg o.m. on 24-h intragastric acidity and plasma gastrin concentration in healthy *H. pylori*-negative volunteers, in a randomized, double-blind, placebo-controlled trial.

MATERIALS AND METHODS

Subjects

Twenty-four healthy non-smoking male volunteers (mean age 23 years, range 20–34 years) were recruited for this randomized, double-blind, placebo-controlled, three-way crossover study. All were negative for *H. pylori* infection, determined by serology and ^{13}C-urea breath test, were within the normal weight range as determined by the Metropolitan Life Insurance Tables and had no clinically significant disease as determined by medical history, physical examination, haematology, biochemistry and urinalysis. Subjects were excluded if they had participated in any clinical trial in the previous 3 months, had taken any medication within 48 h of the start of the trial, had taken any acid-suppressing medication in the previous 7 days, or were felt unlikely to comply with the trial medication or investigation procedures. All subjects gave written informed consent and the study was approved by the Ethical Approval Committee of the Royal Free Hampstead NHS Trust.

Serology

Subjects were initially screened for *H. pylori* infection using a commercially available specific IgG ELISA test (Meridian Diagnostics, Cincinnati, OH). A positive cut-off optical density of ≥ 0.10, measured at 450 nm, was used.

^{13}C-urea breath test

Subjects who had negative serology underwent a ^{13}C-urea breath test (BSIA, Brentford, UK) according to the Standard European Protocol.[20] A result was considered negative if excess $\delta^{13}CO_2$ was greater less 3.5 p.p.m. at 30 min.[21]

Study medication

Subjects were dosed for 8 days on three separate occasions in a randomized fashion with rabeprazole 20 mg (tablet) and placebo omeprazole 20 mg (capsule), omeprazole 20 mg and placebo rabeprazole 20 mg, or placebo rabeprazole 20 mg and placebo omeprazole 20 mg. All medications were taken once daily, at 08.00 hours. There was a washout period of 7 days between each dosing session.

Intragastric acidity and plasma gastrin measurement

Subjects were investigated on six occasions, on the 1st and 8th day of each of the three dosing sessions. On each occasion, subjects were admitted to a research ward after an overnight fast. A 10-French gauge Salem sump nasogastric tube (Sherwood Medical, Petit Rechain, Belgium) was positioned in the stomach. Aliquots (5–10 mL) of intragastric contents were aspirated hourly for the 24 h of the study (08.00–08.00 hours). The pH of each aliquot was immediately measured to the nearest 0.01 pH unit by means of a glass electrode and digital pH meter (Radiometer, Copenhagen, Denmark). The electrode was calibrated with standard

buffers (pH 1.09, 4.01 and 7.00; Radiometer) before and halfway through each batch of samples.

On the 8th day of each dosing session, plasma gastrin was measured hourly from 08.00 to 24.00 hours, then every 2 h thereafter. Blood was collected via a venous cannula into lithium-heparin glass tubes containing 0.2 mL aprotinin (Trasylol; Bayer, Newbury, UK). These tubes were centrifuged immediately, with the plasma transferred to plastic tubes and stored at – 20 °C. All plasma samples from each patient were analysed for gastrin in one batch, by radioimmunoassay using antibody Gas 179 in Professor Bloom's Laboratory at the Hammersmith Hospital, London.[22]

During the studies the subjects were fully ambulant around the ward. The food and environmental conditions for all six 24-h studies were identical and followed the Royal Free Hospital protocol for 24-h studies.[23]

Safety evaluation

All adverse events occurring during the study period were recorded. Pulse and blood pressure measurement, haematological and biochemical evaluation, and urinalysis were performed after each dosing session.

Statistical analysis

A 24-h profile of intragastric pH was obtained for each subject on day 1 and day 8 of dosing. The median 24-h pH and mean percentage time intragastric pH was > 3 and > 4 was calculated for each subject during each dosing session. A 24-h profile of intragastric acidity was obtained for each subject on day 1 and day 8 of dosing, and a 24-h plasma gastrin profile obtained for day 8. Intragastric acidity (mmol/L) was calculated from the intragastric pH by the formula:

$$\text{Intragastric acidity} = (1/\text{antilog}_{10}\ \text{pH}) \times 1000$$

The integrated area under the curve (*AUC*) for each subject's intragastric acidity and plasma gastrin profiles were calculated by the trapezoid rule for both the 24-h and meal-related (morning: 09.00–13.00 hours, afternoon: 13.00–19.00 hours, evening: 19.00–22.00 hours, night-time: 22.00–08.00 hours) time periods.

Differences in *AUC*s and percentage time intragastric pH was > 3 and > 4 were assessed by an analysis of variance (ANOVA) model suitable for a three-period crossover study using SAS for Unix software. The model included the terms for group, subject nested within group, period and study medication effects. Median intragastric pH results were compared using a Wilcoxon matched pairs signed rank test.

For all analyses, P-values ≤ 0.05 were considered significant.

RESULTS

Twenty-three subjects completed the study. One subject withdrew after the first dosing session due to other commitments. The plasma gastrin data during omeprazole dosing was incomplete for one subject. These data were excluded from the analysis.

Day 1 intragastric acidity

The 24-h median and individual integrated intragastric acidity profiles on day 1 of dosing with rabeprazole, omeprazole and placebo are given in Figure 1. The median integrated intragastric acidity was significantly decreased during all time periods for both rabeprazole and omeprazole when compared with placebo (Table 1). Rabeprazole produced a significantly greater decrease in integrated acidity compared with omeprazole for the whole 24-h period (331 vs. 640 mmol.h/L, $P < 0.001$) and for three of the four meal-related time periods (afternoon, evening and night). The percentage decreases in 24-h intragastric acidity compared with placebo were 66% for rabeprazole and 35% for omeprazole. The median 24-h intragastric pH and time spent at pH > 3 and > 4 were significantly greater for rabeprazole compared with both omeprazole and placebo (Table 2, Figure 2). Percentage time intragastric pH was > 3 and > 4 was 54.6% and 44.1%, respectively, during the 24 h following the first dose of rabeprazole, compared with 36.5% and 24.7% for omeprazole and 19.1% and 7.6% for placebo.

Day 8 intragastric acidity and plasma gastrin

The 24-h median and individual integrated intragastric acidity profiles on day 8 of dosing with rabeprazole, omeprazole and placebo are given in Figure 3. The median integrated intragastric acidity was significantly decreased for all time periods for both rabeprazole and omeprazole when compared with placebo (Table 3). There was no significant difference between rabeprazole

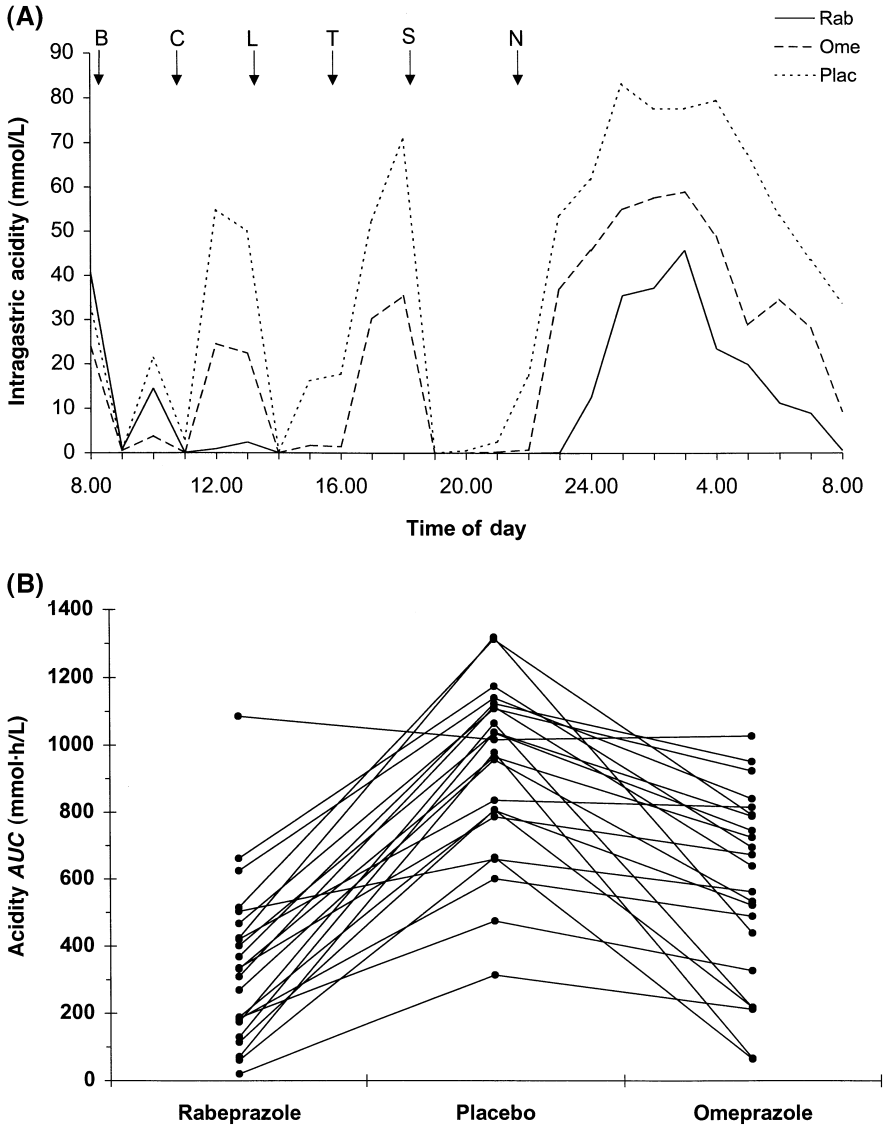

Figure 1. (A) Median 24-h intragastric acidity and (B) integrated 24-h intragastric acidity on day 1 of dosing with rabeprazole (Rab) 20 mg, omeprazole (Ome) 20 mg or placebo (Plac) once daily in 23 healthy subjects. B = breakfast, C = coffee, L = lunch, T = tea, S = supper, N = night-time snack.

and omeprazole for the whole 24-h period, but a significant decrease in acidity was found with rabeprazole for the afternoon and night-time periods. The percentage decrease in 24 h intragastric acidity compared with placebo was 82% for rabeprazole and 76% for omeprazole. The median intragastric pH was significantly greater for both rabeprazole and omeprazole compared with placebo (Table 2). There were no significant differences between the two active drugs. However, the percentage time intragastric pH was > 3 and > 4 were both significantly greater for rabeprazole, 68.6% and 60.3%, respectively, than for omeprazole, 59.4% and 51.4% (Figure 4).

The 24-h median and individual integrated plasma gastrin concentration profiles on day 8 of dosing with rabeprazole, omeprazole and placebo are given in Figure 5. The integrated median plasma gastrin concentration was significantly higher during all time periods for both rabeprazole and omeprazole when compared with placebo (Table 4). Rabeprazole dosing resulted in a significantly higher integrated median plasma gastrin concentration compared with omeprazole,

Table 1. Summary of median (minimum – maximum) intragastric acidity *AUC* (mmol.h/L) for day 1 of dosing (n = 23)

Time period	Rabeprazole	Omeprazole	Placebo
Morning	45[a]	64[a]	139
08.00–13.00	(9–219)	(2–185)	(38–205)
Afternoon	12[a, b]	97[a]	188
13.00–19.00	(0–176)	(0–191)	(41–258)
Evening	0.05[a]	1[a]	13
19.00–22.00	(0–26)	(0–63)	(0.2–63)
Night	163[a, b]	479[a]	617
22.00–08.00	(0.05–733)	(5–744)	(214–916)
24 h	331[a, b]	640[a]	977
08.00–08.00	(20–1086)	(65–1027)	(315–1319)

[a]$P < 0.001$ vs. placebo; [b]$P \leq 0.001$ vs. omeprazole.

for both the meal-related intervals and the total 24-h period (1687 vs. 1085 pmol.h/L, $P < 0.001$).

Drug safety

No serious adverse events were reported during the course of the study. Twenty-four minor ($n = 22$) or moderate ($n = 2$) events were recorded by 17 subjects, none of which resulted in discontinuation of the study medication. At least one adverse event was reported by 4/23 (17%) subjects during rabeprazole dosing, 7/23 (30%) during omeprazole dosing, and 6/23 (26%) during placebo dosing. No clinically important alterations in haematology, biochemistry, urinalysis or vital signs were observed during the course of the study.

DISCUSSION

There are few data on the effects of proton pump inhibitors on intragastric acidity and plasma gastrin concentrations in *H. pylori*-negative individuals. The results of the series of studies by Blum and colleagues, comparing median 24-h pH during omeprazole dosing in *H. pylori* infected and uninfected subjects, makes testing for *H. pylori* infection essential for all further proton pump inhibitor efficacy studies.[13–15] We suggest that data obtained from *H. pylori*-negative subjects will be of greater clinical value than from *H. pylori*-positive subjects. Antisecretory drugs alone are no longer acceptable treatment for the great majority of peptic ulcer disease patients who are infected with *H. pylori*, although it may be necessary for the small numbers of patients who refuse or repeatedly fail *H. pylori* treatment. Today, the main indications for proton pump inhibitor therapy are in the treatment of GERD and, to a lesser extent, in the treatment of *H. pylori*-negative peptic ulcer disease. *H. pylori* infection is not implicated in GERD, indeed there may be a negative association between the two.[24, 25] Infection rates amongst GERD patients will therefore be at the same level as the background population, if not lower. As the prevalence of *H. pylori* decreases in developed countries,[26] so the proportion of *H. pylori* infected GERD patients will continue to decrease. Furthermore, there is evidence that patients with GERD on long-term proton pump inhibitors who are infected with *H. pylori* develop atrophic gastritis at a faster rate than uninfected patients.[27] This has resulted in recommendations that *H. pylori* infection be treated in those patients with GERD who require long-term proton pump inhibitors.[28]

Table 2. Median (interquartile range) 24-h pH on day 1 and day 8 of dosing with rabeprazole 20 mg, omeprazole 20 mg and placebo once daily in 23 healthy volunteers

	Rabeprazole	Omeprazole	Placebo
Day 1	3.2[a, b]	2.0[c]	1.5
	(2.4–4.0)	(1.6–2.5)	(1.3–1.7)
Day 8	4.7[a]	4.2[a]	1.5
	(3.8–4.8)	(2.6–5.0)	(1.4–1.7)

[a]$P = 0.0001$ vs. placebo; [b]$P = 0.0004$ vs. omeprazole; [c]$P = 0.0003$ vs. placebo.

What data there are on the effect of proton pump inhibitors on intragastric acidity and plasma gastrin concentrations in *H. pylori*-negative individuals are very similar to the results of the current study. The median 24-h intragastric pH in *H. pylori*-negative healthy subjects on the 7th day of dosing with omeprazole 20 mg was 4.0 in the original study by Verdú *et al.*,[13] and was 4.2 on the 6th day of dosing in a study by Geus *et al.*;[29] the result in the current study (4.2) is consistent with these previous results. In addition, Geus *et al.* found the percentage time pH was > 3 and > 4 was 68.1% and 53.2%, respectively, again similar to the results (59.4% and 51.5%) in the current study. With regard to rabeprazole, a study involving 24 subjects, of whom 22 were *H. pylori*-negative, demonstrated an 81% decrease in intragastric acidity on day 7 of dosing with 20 mg once daily rabeprazole, compared with the 82% decrease found in the current study.[7] The mean 24-h plasma gastrin concentrations during dosing were also very similar, being 1936 pmol.h/L and 1687 pmol.h/L, respectively, in the two studies.

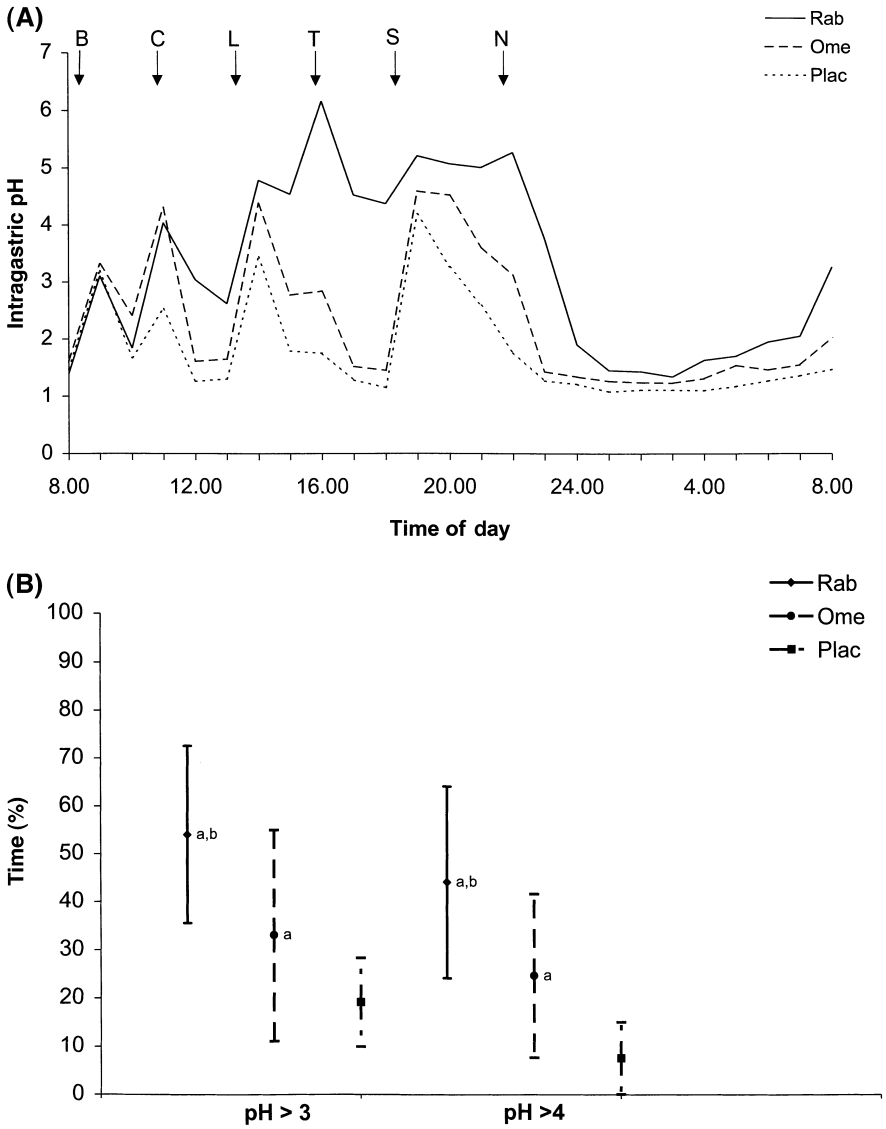

Figure 2. (A) Median 24-h intragastric pH and (B) mean (± s.d.) percentage time that pH was > 3 and > 4 on day 1 of dosing with rabeprazole 20 mg, omeprazole 20 mg or placebo once daily in 23 healthy subjects. [a] $P < 0.001$ vs. placebo, [b] $P < 0.001$ vs. omeprazole.

We have demonstrated that rabeprazole 20 mg once daily has a faster onset of antisecretory activity than omeprazole 20 mg once daily. After a single dose, rabeprazole 20 mg results in a significantly greater decrease in 24-h acidity and nocturnal acidity, and a significantly greater increase in median 24-h pH than omeprazole 20 mg. The time the intragastric pH is > 3 and > 4 is significantly greater for rabeprazole. Our results would also suggest that repeated dosing with rabeprazole 20 mg o.m. may produce greater inhibition of gastric acid secretion than omeprazole 20 mg o.m. Eight days of dosing with rabeprazole resulted in decreased intragastric acidity, compared with omeprazole, for the whole 24-h period and every meal-related time interval. The decrease was statistically significant for the afternoon and night-time periods. Rabeprazole dosing also produced a numerically higher median 24-h pH, with the time intragastric pH was > 3 and > 4 being significantly greater for rabeprazole. These parameters have been shown to be important factors in the healing of duodenal ulcers[30] and oesophagitis,[31] respectively. Also, the 24-h plasma gastrin was significantly greater during rabeprazole dosing. Using an identical protocol for measuring 24-h intragastric

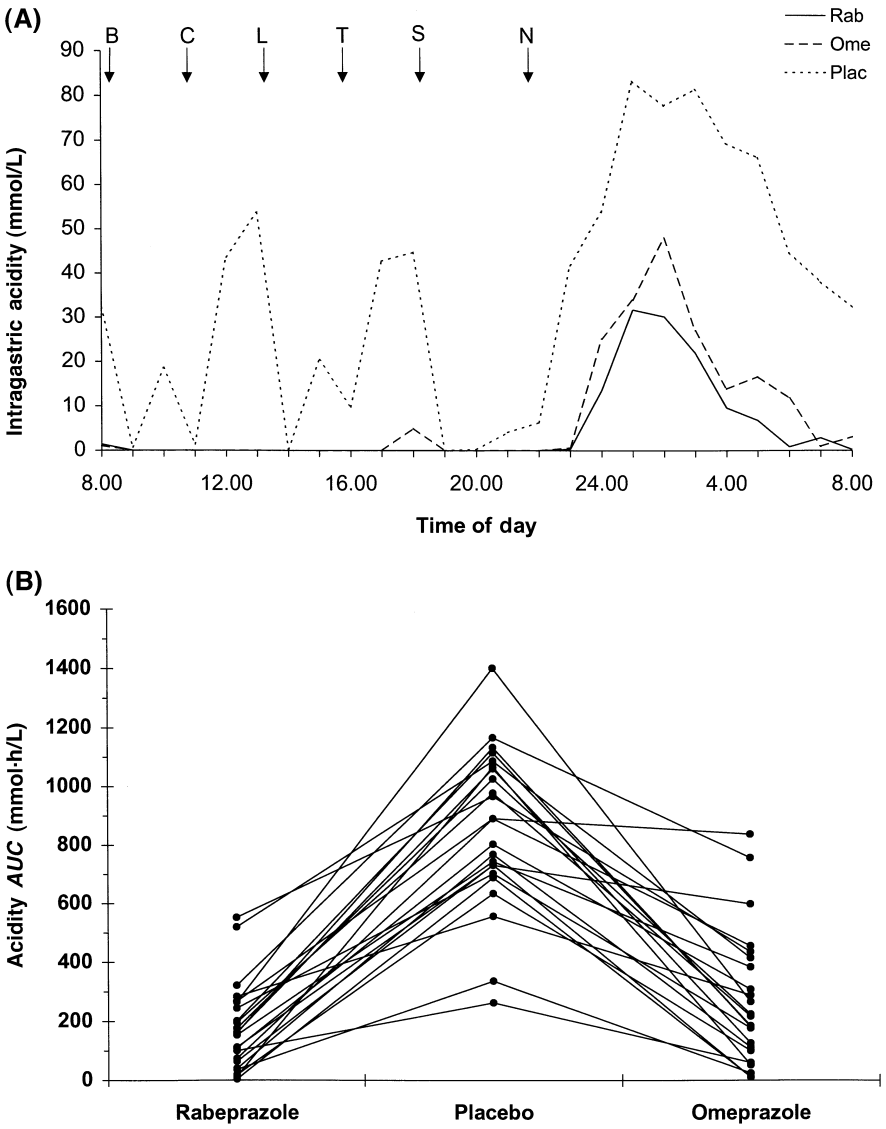

Figure 3. (A) Median intragastric acidity and (B) integrated 24-h intragastric acidity on day 8 of dosing with rabeprazole 20 mg, omeprazole 20 mg or placebo once daily in 23 healthy subjects.

acidity and plasma gastrin, we have demonstrated a clear relationship between a drug-induced decrease in intragastric acidity and an increase in plasma gastrin concentration,[32] a relationship confirmed by other authors also using the aspiration technique.[33]

The differences in antisecretory activity after single doses may be due to different pharmacokinetic properties. As with other proton pump inhibitors, both have a plasma half-life of about 1 h in young healthy subjects, but because of covalent binding to H^+,K^+-ATPase, both have a much longer duration of action. Therefore the maximal concentration (C_{max}), and particularly the area under the plasma concentration curve (*AUC*), are more important determinants of efficacy.[34] Both the C_{max} and *AUC* for omeprazole increase after repeat oral doses compared with a single oral dose. In healthy volunteer studies, the increases for omeprazole 20 mg orally are 41–69% for *AUC* and 32–51% for C_{max}, after 5–7 days of dosing.[35, 36] This is thought to be due to decreased acid degradation of acid-resistant enteric-coated granules and/or reduced hepatic metabolism.[11] No such increase is seen after repeated dosing of rabeprazole 20 mg for 7 days.[37] After repeated dosing, the pharmacokinetic data for the two drugs are similar.

It remains unclear why *H. pylori* infection enhances the antisecretory effect of omeprazole. Blum's group

Table 3. Summary of median (minimum – maximum) intragastric acidity *AUC* (mmol.h/L) for day 8 of dosing ($n = 23$)

Time period	Rabeprazole	Omeprazole	Placebo
Morning	4.98[a]	5.13[a]	122
08.00–13.00	(0–50)	(0–118)	(19–193)
Afternoon	0.8[a, b]	5[a]	150
13.00–19.00	(0–8)	(0–148)	(69–332)
Evening	0.03[a]	0.05[a]	10
19.00–22.00	(0–8)	(0–149)	(0.1–88)
Night	153[a, b]	200[a]	610
22.00–08.00	(4–473)	(0.5–663)	(158–1081)
24 h	160[a]	218[a]	890
08.00–08.00	(4–553)	(10–837)	(263–1493)

[a]$P \leq 0.001$ vs. placebo; [b]$P < 0.05$ vs. omeprazole.

have concluded that the increased pH produced by omeprazole during *H. pylori* infection is likely to be due to neutralizing substances produced by *H. pylori*.[38] Other authors have suggested that substances produced by the organism itself, or as a result of the associated inflammatory response, impair parietal cell secretory function.[39–42] Another potential mechanism concerns the activity of omeprazole at the level of the proton pump. Blum's group have shown that curing *H. pylori* augments the antisecretory activity of ranitidine, an H_2-receptor antagonist, although the effect is markedly less pronounced than with omeprazole.[43] This would suggest that the proton pump itself is the affected target.

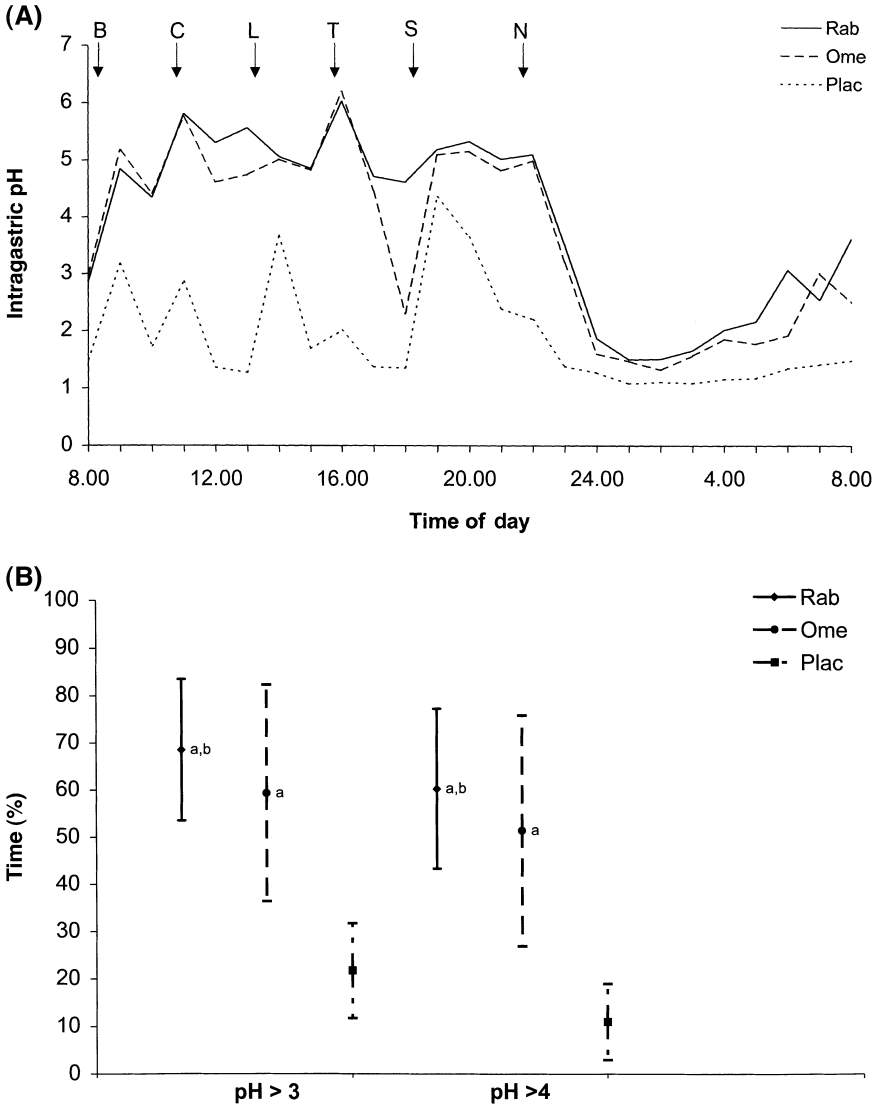

Figure 4. (A) Median 24-h intragastric pH and (B) mean (± s.d.) percentage time that pH was > 3 and > 4 on day 8 of dosing with rabeprazole 20 mg, omeprazole 20 mg or placebo once daily in 23 healthy subjects. [a] $P < 0.001$ vs. placebo, [b] $P < 0.001$ vs. omeprazole.

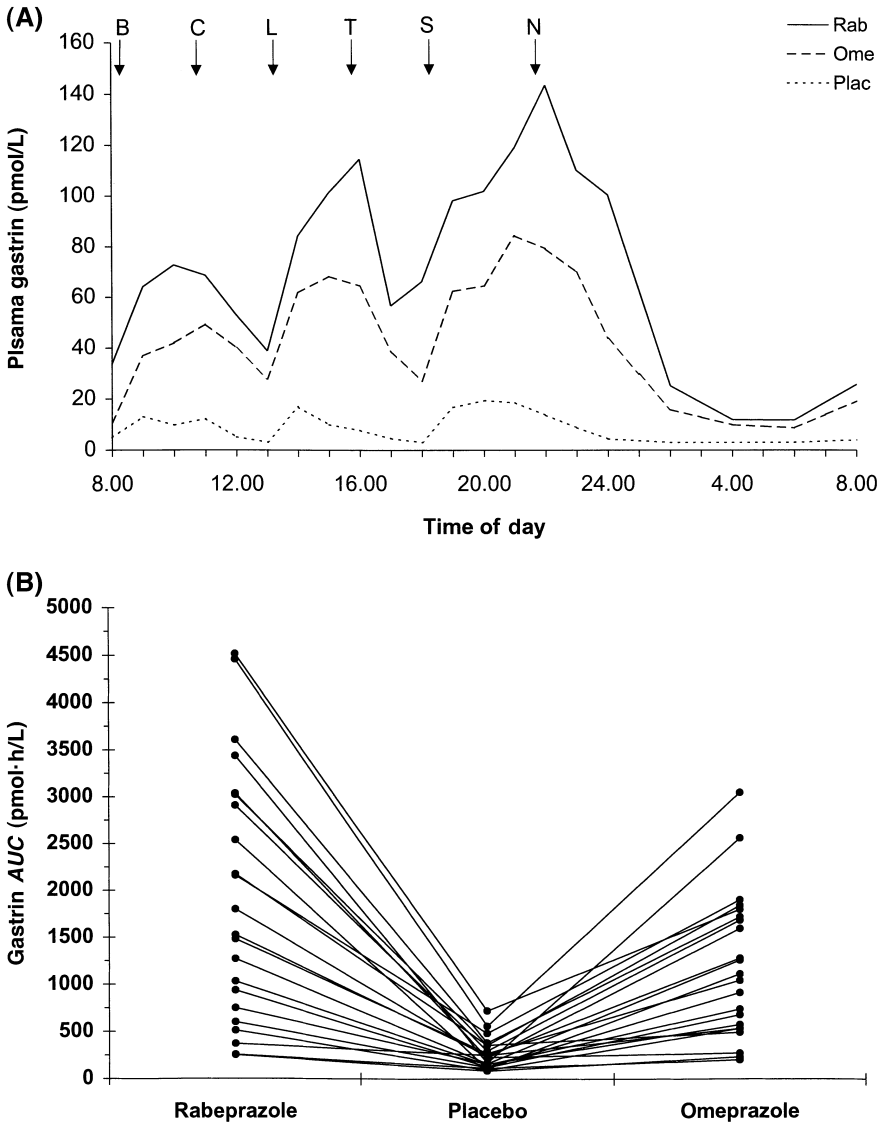

Figure 5. (A) Median plasma gastrin concentration and (B) integrated 24-h plasma gastrin concentration on day 8 of dosing with rabeprazole 20 mg, omeprazole 20 mg or placebo once daily in 23 healthy subjects.

All proton pump inhibitors are lipophilic, weak bases which cross parietal cell membranes readily to enter the highly acidic parietal cell secretory canaliculus. At lower pH, proton pump inhibitors become protonated and therefore no longer lipophilic. Once trapped in the secretory canaliculus, the drugs are concentrated, activated by acid to the sulphenamide form, and are able to inhibit H^+,K^+-ATPase by binding covalently to the extracytoplasmic cysteine residues of the enzyme's α subunit.[34] Recent *in vitro* studies, using vesicular preparations of the hog gastric H^+,K^+-ATPase under acid transporting conditions, have demonstrated a faster rate of inhibition of ATPase and acid transport for rabeprazole than omeprazole, lansoprazole or pantoprazole.[44] The rates of inhibition correlate with the relative acid stability of the various drugs. Rabeprazole converts more rapidly to the activated sulphenamide form than the other proton pump inhibitors at neutral and acid pH, and therefore inhibits H^+,K^+-ATPase more rapidly.

The plasma half-lives of all proton pump inhibitors are relatively short. Therefore, the time available for these drugs to accumulate in the parietal canaliculus, form the sulphenamide, and bind to available active proton pumps is short. Conditions which increase parietal cell

Table 4. Summary of median (minimum – maximum) plasma gastrin concentration *AUC* (pmol.h/L) for day 8 of dosing ($n = 22$*)

Time period	Rabeprazole	Omeprazole	Placebo
Morning	325[a, b]	227[a]	53
08.00–13.00	(47–859)	(41–476)	(15–148)
Afternoon	607[a, b]	328[a]	68
13.00–19.00	(71–1498)	(53–991)	(20–264)
Evening	336[a, b]	234[a]	57
19.00–22.00	(45–954)	(38–592)	(15–213)
Night	434[a, c]	272[a]	47
22.00–08.00	(77–1819)	(53–1113)	(30–149)
24 h	1687[a, b]	1085[a]	226
08.00–08.00	(252–4523)	(204–3060)	(86–722)

[a]$P \leq 0.001$ vs. placebo; [b]$P \leq 0.001$ vs. omeprazole; [c]$P = 0.003$ vs. omeprazole.
*Excluding incomplete data set from one subject.

stimulation, such as hypergastrinaemia, may have profound effects on the antisecretory activity of proton pump inhibitors. For example, stimulation of parietal cells with pentagastrin infusion considerably increases the antisecretory activity of omeprazole.[45] Increased gastrin secretion may therefore explain the effect of *H. pylori* infection on the antisecretory activity of omeprazole, because infected individuals have a significantly higher 24-h plasma gastrin concentration than those not infected,[46] with the highest being seen in those patients with duodenal ulcers.[47] Once *H. pylori* infection is cured, gastrin levels decrease to those found in uninfected individuals.

There are currently no published data for other proton pump inhibitors and the effect of cure of *H. pylori* infection on antisecretory activity. Therefore, it remains to be seen if cure of *H. pylori* infection has any discernible effect on the antisecretory activity of rabeprazole. It may be that because of its already rapid activation, parietal cell stimulation by gastrin will have little, if any, effect on rabeprazole's antisecretory activity. There is also a lack of comparative data on the efficacy of proton pump inhibitors in proven *H. pylori*-negative individuals. In the only other reported comparative study in *H. pylori*-negative healthy subjects, no differences were found in median 24-h pH between omeprazole and lansoprazole in standard once daily doses.[29] We have demonstrated that rabeprazole 20 mg once daily has a significantly faster onset of antisecretory activity than omeprazole 20 mg once daily. After 8 days the differences in intragastric pH > 3 and > 4 holding times persisted, but there was no significant difference in 24-h acidity.

ACKNOWLEDGEMENTS

This study was supported by a grant from EISAI Ltd, London, UK.

REFERENCES

1 Morii M, Hamatani K, Takeguchi N. The proton pump inhibitor E3810 binds to the N-terminal half of the α-subunit of gastric H^+/K^+-ATPase. Biochem Pharmacol 1995; 49: 1729–34.
2 Nochi S, Yokohama Y, Narugawa M, *et al*. Mechanism of inhibition of H^+/K^+ ATPase by E3810. Chem Pharm Bull 1996; 44: 552–8.
3 Fujisaki H, Shibata H, Oketani K, *et al*. Inhibitions of acid secretion by E3810 and omeprazole, and their reversal by glutathione. Biochem Pharmacol 1991; 42: 321–8.
4 Fujisaki H, Shibata H, Oketani K, *et al*. Effects of the proton pump inhibitor, E3820, on gastric secretion and gastric duodenal ulcers or erosions in rats. Drug Invest 1991; 3: 328–32.
5 Kovacs EJ, Syntnik B, Humphries TJ, Walsh JH. A low dose of a new proton pump inhibitor, LY307640 (E3810) effectively inhibits acid secretion in humans. Gastroenterology 1996; 110(4): A240(Abstract).
6 Robinson M, Maton PN, Rodruigez S, Greenwood B, Humphries TJ. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1997; 11: 973–80.
7 Blanshard C, Millson C, Sercombe J, Pounder RE. The effects of rabeprazole on 24-hour intragastric acidity and plasma gastrin concentration in healthy subjects. Gut 1996; 39(Suppl. 3): A47(Abstract).
8 Cloud ML, Enas N, Humphries T, Bassion S, and the Rabeprazole Study Group. Results of three placebo-controlled clinical trials in duodenal ulcer, gastric ulcer and gastroesophageal reflux disease. Dig Dis Sci 1998; 43: 993–1000.
9 Humphries TJ, Spera A, Brieter J, *et al*. Rabeprazole sodium once daily is superior to ranitidine 150 mg bid in the healing of active duodenal ulcer. Gastroenterology 1997; 112(4): A154(Abstract).
10 Humphries T, Spera AC, Breiter J, *et al*. Rabeprazole sodium (E3810) once daily is superior to ranitidine 150 mg qid in the healing of erosive or ulcerative gastroesophageal reflux disease. Gastroenterology 1996; 110(4): A240(Abstract).
11 McTavish D, Buckley MM-T, Heel RC. Omeprazole: an updated review of its pharmacology and therapeutic use in acid related disorders. Drugs 1991; 42: 138–70.
12 van der Hulst RWM, Keller JJ, Rauws EAJ, Tytgat GNJ. Treatment of *Helicobacter pylori* infection: A review of world literature. Helicobacter 1996; 1: 6–19.
13 Verdú EF, Armstrong D, Fraser R, *et al*. Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. Gut 1995; 36: 539–43.
14 Verdú EF, Armstrong D, Idström J-P, *et al*. Effect of curing *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. Gut 1995; 37: 743–8.
15 Labenz J, Tillenburg B, Peitz U, *et al*. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology 1996; 110: 725–32.

16 Cederberg C, Röhss K, Lundborg P, Olbe L. Effect of once daily intravenous and oral omeprazole on 24-hour intragastric acidity in healthy subjects. Scand J Gastroenterol 1993; 18: 179–84.
17 Dekkers CPM, Beker JA, Thjodleifsson B, Cabryelewicz A, Bell NE, Humphries TJ, and the European Rabeprazole Study Group. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer—a European multicentre study. Aliment Pharm Ther 1998; 12: 789–795.
18 Dekkers CPM, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Rabeprazole sodium 20 mg once daily is similar to omeprazole 20 mg once daily in the healing of gastric ulcer. Gastroenterology 1997; 112(4): A99(Abstract).
19 Thjodleifsson B, Beker JA, Dekkers CPM, *et al*. Omeprazole sodium 20 mg once daily is similar to omeprazole 20 mg once daily in the treatment of ulcerative GERD. Gastroenterology 1997; 112(4): A312(Abstract).
20 Logan RPH, Dill S, Bauer FE, *et al*. The European ^{13}C-UBT for the detection of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1991; 3: 915–21.
21 Johnston BJ, Levi S, Johnson P. Cut-off point for the ^{13}C-urea breath test. Gastroenterology 1996; 110(4): A144(Abstract).
22 Bryant MG, Adrian TE. Gastrin. .In: Bloom SR, Long RG, eds. Radioimmunoassay of Gut Regulatory Peptides. London: Saunders, 1982: 51–9.
23 Pounder RE, Lanzon-Miller S, Smith JTL, *et al*. Royal Free Protocol for 24-hour intragastric acidity and plasma gastrin concentration. Dig Dis 1990; 8(Suppl. 1): 10–1
24 Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barretts's oesophagitis. Gut 1997; 40: 9–13.
25 Mihara M, Haruma K, Kamada T, *et al*. Low prevalence of *Helicobacter pylori* infection in patients with reflux esophagitis. Gut 1996; 39(Suppl. 2): A94(Abstract).
26 Parsonnet J. The incidence of *Helicobacter pylori* infection. Aliment Pharmacol Ther 1995; 9(Suppl. 2): 45–51.
27 Kuipers EJ, Lundell L, Klinkenberg-Knol EC, *et al*. Atrophic gastritis and *Helicobacter pylori* in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med 1996; 334: 1018–22.
28 Anon. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. European Helicobacter Pylori Study Group. Gut 1997; 41: 8–13.
29 Geus WP, Mulder PGH, Nicolai JJ, Van der Boomgaard DM, Lamers CBHW. Acid-inhibitory effects of omeprazole and lansoprazole in *Helicobacter pylori*-negative healthy subjects. Aliment Pharmacol Ther 1998; 12: 329–35.
30 Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression in healing duodenal ulcer? A model of the relationship between ulcer healing and acid suppression. Gastroenterology 1990; 99: 345–51.
31 Bell NJ, Burget D, Howden C, Wilkinson J, Hunt RH. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992; 51(Suppl. 1): 56–67.
32 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al*. Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987; 1: 239–51.
33 Lind T, Cederberg C, Idström J-P, Lönroth H, Olbe L, Lundell L. 24-hour intragastric acidity and plasma gastrin during long-term treatment with omeprazole or ranitidine in patients with reflux esophagitis. Scand J Gastroenterol 1991; 26: 620–6.
34 Huber R, Kohl B, Sachs G, Senn-Bilfinfinger J, Simon WA, Sturm E. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol Ther 1995; 9: 363–78.
35 Andersson T, Cederberg C, Heggelund A, Lundborg P. The pharmacokinetics of single and repeated once-daily doses of 10, 20 and 40 mg omeprazole as enteric-coated granules. Drug Invest 1991; 3: 45–52.
36 Hartmann M, Thieß U, Huber R, *et al*. Twenty-four-hour intragastric pH profiles and pharmacokinetics follwoing single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole. Aliment Pharmacol Ther 1996; 10: 359–6.
37 Yasuda S, Ohnishi A, Ogawa T, *et al*. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int J Clin Pharmacol Ther 1994; 32: 466–73.
38 Verdú EF, Armstrong D, Idström J-P, *et al*. Intragastric pH during treatment with omeprazole: role of *Helicobacter pylori* and *H. pylori*-associated gastritis. Scand J Gastroenterol 1996; 31: 1551–6.
39 Cave DR, Vargas M. Effect of *Campylobacter pylori* protein on acid secretion by parietal cells. Lancet 1989; ii: 187–9.
40 Beil W, Birkholz C, Wagner S, Sewing K-F. Interaction of *Helicobacter pylori* and its fatty acids with parietal cells and H^+/K^+-ATPase. Gut 1994; 35: 1176–80.
41 Gillen D, Wirz A, McColl KEL. Degree of acid suppression of gastric acid secretion by omeprazole is related to *H. pylori* status. Gastroenterology 1997; 112: A126 (Abstract).
42 Healey ZV, Bliss P, Arebi N, Hussain Z, Atherton J, Calam J. The acid inhibitory actions of *Helicobacter pylori* and IL1β on isolated rabbit parietal cells are additive to that of omeprazole. Gut 1997; 41(Suppl. 3): A112(Abstract).
43 Labenz J, Tillenburg B, Peitz U, *et al*. Effect of curing *Helicobacter pylori* infection on intragastric acidity during treatment with ranitidine in patients with duodenal ulcer. Gut 1997; 41: 33–66.
44 Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. J Biol Chem 1997; 272: 22438–46.
45 De Graef J, Woussen-Colle MC. Influence of the stimulation state of the parietal cells on the inhibitory effect of omeprazole on gastric acid secretion in dogs. Gastroenterology 1986; 91: 333–7.
46 Smith JTL, Pounder RE, Nwokolo CU, *et al*. Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with *Helicobacter pylori*. Gut 1990; 31: 522–5.
47 El-Omar EM, Penman ID, Ardill JES, Chittajallu RS, Howie C, McColl KEL. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. Gastroenterology 1995; 109: 681–91.