PAPERS

Effect of curing *Helicobacter pylori* infection on intragastric pH during treatment with omeprazole

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Abstract

It has been shown that omeprazole treatment produces higher intragastric pH values in *Helicobacter pylori* positive subjects than in *H pylori* negative subjects. This study aimed to investigate the effect of curing *H pylori* on the intragastric pH in both the presence and absence of omeprazole therapy. Twenty four hour intragastric pH recordings were performed before and after a one week course of omeprazole (20 mg once daily) in 18 *H pylori* positive subjects and were repeated after the infection had been cured. In the absence of omeprazole, the total 24 hour pH values before cure did not differ from those afterwards. During omeprazole treatment the 24 hour pH values were much higher before (median (95% CI) 5.4: 4.3, 6.0), than after cure of infection (3.6: 2.1, 4.4; $p < 0.001$). The omeprazole induced fall in H^+ activity before cure of *H pylori* did not, however, differ from that afterwards. It is concluded that the apparently greater antisecretory effect of omeprazole during *H pylori* infection may be a result of the production of acid neutralising compounds by the *H pylori*. Although a direct interaction between *H pylori* and omeprazole cannot be excluded, it seems unlikely.

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Our observation that omeprazole produced higher intragastric pH values in *Helicobacter pylori* infected than in uninfected subjects¹ suggests that there may be a direct interaction between *H pylori* infection and omeprazole. Our findings were based, however, on a comparison of two separate groups of subjects and it is therefore arguable that the difference in response to omeprazole might have been related, for example, to a difference in susceptibility to *H pylori* infection. If this had been the case, cure of *H pylori* infection would not have produced a change in the observed effect of omeprazole. We therefore investigated the effect of omeprazole on intragastric pH in subjects before and after cure of *H pylori* infection.

We tested the hypotheses that intragastric pH in the absence of omeprazole administration is unchanged by the cure of *H pylori* and that omeprazole treatment produces lower intragastric pH values after *H pylori* infection has been cured.

Methods

STUDY POPULATION

Eighteen *H pylori* positive subjects (11 men, seven women, aged 22-40 years) participated in the study. All were healthy, with no history of gastrointestinal disease or other illness and no current gastrointestinal symptoms. At the time of enrolment, subjects took no medication except oral contraceptives or paracetamol. Subjects were not included in the study if they had a history of alcohol or drug abuse. Smokers were not excluded but they were asked to refrain from smoking during the pH studies. Subjects in whom gastroesophageal reflux disease or peptic ulcer disease were diagnosed at entry were not included in the study. All subjects gave written, informed consent, and the study was conducted according to the declaration of Helsinki. The protocol was approved by the local ethical committee.

PROTOCOL

Subjects with a positive ¹³C urea breath test and a serology positive enzyme-linked immunosorbent assay (ELISA, Roche, Switzerland) for *H pylori* were included. Subjects underwent upper gastrointestinal endoscopy (Olympus Q20, Olympus, Volketswil, Switzerland) and biopsy specimens were taken for rapid urease test and histology. Fasting blood samples were taken the next morning for serum gastrin, pepsinogen I (PGI), and pepsinogen II (PGII) assays. A 24 hour gastric pH recording was performed the day before omeprazole treatment was started. On day 8 of omeprazole treatment, the pH recording, ¹³C urea breath test, and *H pylori* serology were repeated. To standardise the protocol, all subjects received a second week of omeprazole treatment to allow repetition of any unsatisfactory pH recordings before starting *H pylori* antimicrobial therapy. The two week course of antimicrobial therapy was followed, after a further four weeks, by a ¹³C urea breath test. If the breath test was negative, an

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Figure 1: Time course of the study protocol in weeks; pH=24 hour pH recording. Omeprazole was given in a dose of 20 mg once daily.

endoscopy was performed and biopsy specimens were obtained for rapid urease test and histology. The following day, sera were obtained for gastrin and PG assays. A pH recording was performed the day before starting the second course of omeprazole treatment. A final pH recording was performed on day 8 of omeprazole administration. Sera for *H pylori* IgG antibodies were obtained after the last pH recording (Fig 1).

OMEPRAZOLE MEDICATION

Omeprazole (Astra Hässle AB, Sweden) was taken orally as a single morning dose of 20 mg at 09:15, 30 minutes before breakfast.

ANTIMICROBIAL THERAPY FOR *H PYLORI* INFECTION

The first eight subjects received amoxycillin (1 g twice daily) and omeprazole (60 mg twice daily) for 14 days. Subjects with persistent *H pylori* infection and the remaining 10 subjects received amoxycillin (1 g twice daily), clarithromycin (500 mg twice daily), and omeprazole (40 mg twice daily) for 14 days. It was planned to withdraw subjects who remained positive on testing for *H pylori* after the second course of antimicrobial treatment.

24 HOUR pH-METRY

Subjects arrived in the laboratory at 08:00, after an overnight fast. The pH electrode was inserted transnasally under local anaesthesia and positioned fluoroscopically, so that the electrode was located in the corpus, 5 cm distal to the cardia. Recordings started at 09:00 and three standard meals,² prepared at the hospital, were provided for all subjects. After eating breakfast at 09:45, the subjects returned home with instructions to have lunch at 13:30 and supper at 19:30. Tap water and still mineral water were allowed ad libitum but other beverages were not permitted. Subjects retired at 21:30 and awoke at 06:00 to return to the laboratory by 08:30 the next day. The position of the pH electrode was checked fluoroscopically before its removal at 09:00. Subjects were asked to use the event marker on the data logger to mark the start and the end of each meal, the times at which they went to bed

and got up, and the occurrence of any other significant event.

For all recordings, a glass pH electrode with built-in reference electrode (MIC, Ingold 440-M3, Urdorf, Switzerland) was connected to a data logger (Gastrograph, Mark III, MIC, Solothurn, Switzerland); the pH electrode was calibrated before each recording using standard buffer solutions of pH 1.67 and 7.00 (Ingold, Urdorf, Switzerland). At the end of each recording, data were transferred to a personal computer for analysis (MIC, Solothurn, Switzerland).

¹³C UREA BREATH TEST AND SEROLOGY FOR *H PYLORI* INFECTION

Two fasting baseline breath samples were collected just before the subjects ate a standardised breakfast. Thereafter, the subjects took 100 mg of ¹³C urea dissolved in 200 ml of water and breath samples were collected at 20 and 60 minutes. The ratio of ¹³C/¹²C was measured by mass spectrometry. The difference between the baseline and test ratios was compared with a reference value and the results were expressed as excess delta ¹³CO₂ per mil (excess δ ‰), given a measure of increased urease activity.^{3,4} An excess δ ‰ value of >5 was considered to be positive for *H pylori* infection.

Fasting blood samples from each subject were collected for determination of anti-*H pylori* antibodies. Sera were separated by centrifugation at 4°C for 10 minutes, and stored at -80°C for later analysis. *H pylori* antibodies were measured by a specific ELISA (Roche). The test was defined as positive for *H pylori* infection if a value >10 U/ml was obtained.

ENDOSCOPIC BIOPSIES

Three biopsy specimens were obtained from the corpus and three from the antrum. Two biopsies from each location were placed in 10% buffered formalin for histological examination. All samples were examined by the same pathologist (MS) and processed in a standardised manner. Each biopsy specimen was stained with haematoxylin and eosin to grade gastritis and with the Warthin-Starry technique to detect *H pylori* infection. One biopsy specimen from each site was used to perform a rapid urease test (Jatrox-Hp-Test, Röhn Pharma GmbH, Weiterstadt, Germany). A change in colour from yellow to pink within 24 hours was taken to be a positive result indicative of *H pylori* infection.

HISTOLOGY

The presence of gastritis in the antrum and in the corpus was classified according to a modified Sydney system.⁵ *H pylori* density, lymphocyte and plasma cell infiltrate density, polymorphonuclear leukocyte infiltrate density, replacement of foveolar epithelium by regenerative epithelium, and mucus depletion were graded on a five point scale. Their sum

yielded the gastritis score for the antrum and for the corpus. In addition, mucosal atrophy and intestinal metaplasia were sought in all biopsy specimens.

GASTRIN AND PEPSINOGENS ANALYSIS

Commercial radioimmunoassay kits were used to determine fasting gastrin (Zodiac, Sorin Biomedica, Italy), PGI and PGII (Pepsik, Pepsi-II K, Sorin Biomedica, Italy). Reference values for the laboratory performing the analyses (Olten Med, Olten, Switzerland) were <50 pmol/l for gastrin, 20 to 80 ng/ml for PGI, and 4 to 20 ng/ml for PGII. The ratio PGI:PGII was calculated for all measurements.

DATA ANALYSIS AND STATISTICAL EVALUATION

The time intervals for analysis were predefined as follows: entire recording (09:00–09:00), combined meal time periods (09:45–11:45, 13:30–15:30, 19:30–21:30), night-time (22:00–06:00), early night-time (22:00–02:00), late night-time (02:00–06:00), and the remaining combined non-meal daytime period. Median pH values for the entire recording and for each of the predefined time periods were calculated.

Median H^+ activities (mM) were calculated from the recorded pH values ($10^3 \times 10^{-pH}$).

The omeprazole induced falls in H^+ activity were calculated as $((10^{-pH} \text{ without omeprazole}) - (10^{-pH} \text{ with omeprazole}))$ before and after cure of *H. pylori* infection.

All data are presented as group median values with 95% confidence intervals (95% CI) and all statistical testing was conducted using the Wilcoxon rank test for paired samples.

Figure 2: Mean 24 hour pH curves ($n=18$) in the absence of omeprazole treatment (upper panel) and during omeprazole treatment (lower panel), before (thick line) and four weeks after cure of *H. pylori* infection (thin line).

Results

Eighteen subjects completed the study. Mild diarrhoea was reported by two subjects who were taking omeprazole and amoxycillin and by one subject who was taking omeprazole, amoxycillin, and clarithromycin. One subject reported taste disturbance during omeprazole, amoxycillin, and clarithromycin administration. No adverse event prompted withdrawal of subjects from the study and all symptoms resolved after stopping treatment.

In one subject, one recording had to be repeated within 24 hours of the initial recording because of electrode failure.

Omeprazole and amoxycillin cured the *H. pylori* infection in five of eight subjects. Omeprazole, amoxycillin, and clarithromycin cured the *H. pylori* infection in the three remaining subjects with persistent infection and in the 10 subsequent subjects for whom this was the initial treatment regimen. Thus, no subject had to be withdrawn after the second antimicrobial treatment because of persistent *H. pylori* infection.

INTRAGASTRIC pH-METRY

In the absence of omeprazole, the mean 24 hour pH plots show that nocturnal pH was higher during *H. pylori* infection than after cure (Fig 2). During omeprazole treatment, the gastric pH was higher throughout the entire recording before the cure of *H. pylori* infection. Without omeprazole, the median 24 hour pH values before the cure of *H. pylori* infection (1.3; 95% CI: 1.2, 1.4) did not differ from those observed after cure (1.2; 1.0, 1.3) (Fig 3). There was, however, a fall in the late nocturnal pH from 1.6 (1.3, 4.3) before cure to 1.2 (0.9, 1.5) after cure ($p=0.005$) (Table I). Omeprazole treatment produced a higher median 24 hour gastric pH before cure (5.4; 4.3, 6.0) than afterwards (3.6; 2.1, 4.4; $p<0.001$), and this difference was observed during all predefined time periods (Table I).

The H^+ activity observed during omeprazole treatment before *H. pylori* cure was lower than that observed afterwards. However, the omeprazole induced fall in H^+ activity before cure was similar to that produced afterwards (Table II).

BREATH TEST AND SEROLOGY RESULTS

Before cure of *H. pylori* infection, negative breath test results were observed in three subjects one week after omeprazole treatment (Fig 4: upper panel, left). However, there was no difference between the excess δ % values observed during screening and those observed after omeprazole therapy ($p=0.3$).

Serology titres were similar during screening after the first week of omeprazole treatment ($p=0.9$), and were significantly lower after cure of *H. pylori* ($p=0.0009$). Serology titres at four weeks were negative in only one cured subject (Fig 4: upper panel, right).

ENDOSCOPIC AND HISTOLOGICAL FINDINGS

Before cure, one subject had an isolated

Figure 3: Median 24 hour pH values ($n=18$) in the absence of omeprazole treatment and during omeprazole treatment, before and four weeks after the cure of *H pylori* infection. Intra-gastric pH values during omeprazole treatment were lower after cure ($p<0.001$). Horizontal bars show group median pH values.

Figure 4: Upper panel: serology titres and excess delta (δ) ^{13}C % values at entry, after one week of omeprazole treatment, and four weeks after cure of *H pylori*. Serology titres and excess δ ^{13}C % were similar at pre-entry screening (S) and after one week of omeprazole but significantly lower four weeks after cure of *H pylori* infection. Lower panel: total *H pylori* associated gastritis scores in the corpus and in the antrum during *H pylori* infection and four weeks after cure of *H pylori* infection. Both antral and corpus gastritis improved significantly after cure. Horizontal bars show medians.

erosion in the corpus. After cure, no epithelial breaks were observed. Giant folds were not observed in any subject during endoscopies. The total score of *H pylori* associated gastritis decreased in both the antrum and corpus four weeks after stopping the antimicrobial therapy ($p<0.001$; Fig 5). Neither atrophy nor intestinal metaplasia were found in any of the biopsy specimens.

GASTRIN AND PEPSINOGENS

Before cure, all subjects had plasma gastrin values within the normal range and nine subjects had PGI values above 80 ng/l. Four weeks after antimicrobial treatment for *H pylori* infection, gastrin, PGI, and PGII median values were decreased (Table III). In three subjects, gastrin values did not change after the cure of *H pylori*. PGI values were unchanged in three subjects, and PGII values were unchanged in one subject after cure. PGI and PGII values were, however, within the normal ranges in these cases.

Discussion

In the present study, we have performed 24 hour intra-gastric pH recordings to assess the effect of curing *H pylori* infection on intra-gastric acidity. We have observed that during omeprazole treatment intra-gastric pH was higher before the cure than afterwards. We, like other authors, observed falls in serum gastrin and pepsinogen after cure of *H pylori* infection⁶⁻⁹ but no significant changes in spontaneous acidity.^{7 10}

Gastric acid output studies performed before and after cure of *H pylori* infection have yielded contradictory results.^{6 7 11-13} Cure of *H pylori* infection has been reported to decrease basal gastric acid output^{11 13} but it may also abolish the production of buffer substances by both *H pylori* and the host, leading to an overall increase in gastric acidity. It should be noted that pH-metry measures net acidity, which is a product of many factors, whereas output studies estimate the ability of the stomach to produce acid without assessing the effect of additional buffers or modifying factors. Therefore, different measuring parameters of acid secretion studies and pH-metry studies may account for the apparently discrepant conclusions derived from these two complementary techniques.

The omeprazole induced fall in H^+ activity before cure was similar to that afterwards, and this finding held true for the entire 24-hour recording period (Table II). This suggests that *H pylori* infection does not have a direct effect on the action of omeprazole. It is more likely that the *H pylori* infection has other effects which modify net gastric acidity and that these effects are more evident during omeprazole therapy. There are several possible explanations for this apparent lower effect of omeprazole on the 24 hour profile after cure of *H pylori* infection.

One possible explanation for our findings relates to the observation that *H pylori*

TABLE I Group median pH values (95% confidence intervals) for predefined time periods before and after cure of *Helicobacter pylori* infection, in the absence of omeprazole treatment (no omeprazole) and during omeprazole treatment

Time	No omeprazole		Omeprazole	
	H pylori +ve	H pylori -ve	H pylori +ve	H pylori -ve
24 h	1.3 (1.2, 1.4)	1.2 (1.0, 1.3)	5.4 (4.3, 6.0)	3.6 (2.1, 4.4)
M	1.6 (1.3, 1.8)	1.4 (1.3, 1.9)	4.9 (4.5, 5.7)	4.3 (3.5, 4.5)
D	1.2 (0.9, 1.3)	1.2 (1.0, 1.5)	5.0 (3.6, 6.5)	3.9 (2.0, 4.2)
N	1.3 (1.2, 1.6)	1.1 (1.0, 1.4)	6.1 (4.1, 6.8)	3.2 (1.6, 3.5)
EN	1.1 (1.1, 1.3)	1.1 (0.9, 1.2)	3.2 (1.9, 5.1)	1.6 (1.3, 2.0)
LN	1.6 (1.3, 4.3)	1.2 (0.9, 1.5)	6.9 (6.4, 7.1)	4.8 (2.2, 6.2)

H pylori +ve: before cure of *H. pylori* infection, H pylori -ve: one month after cure of *H. pylori* infection. M=combined meal time periods (09:45–11:45, 13:30–15:30, 19:30–21:30), D=day-time period (the remaining combined non-meal daytime intervals), N=night-time (22:00–06:00), EN=early night-time (22:00–02:00), LN=late night-time (02:00–06:00).

infection may be associated with mucosal atrophy.¹⁴ A consequent decrease in the G-cell population could reduce stimulation of gastric acid secretion, thereby increasing the effect of omeprazole in *H. pylori* positive subjects. However, there is no convincing evidence that cure of *H. pylori* infection leads to a rapid regression of atrophy or metaplasia,^{15, 16} and in the present study there was no evidence of mucosal atrophy or intestinal metaplasia in any subject. It has recently been suggested that patients with enlarged gastric body folds and *H. pylori* infection have lower acid secretion beforehand than after cure.¹⁷ However, in the present study gastric folds were not enlarged.

Another possible explanation is that *H. pylori* infection itself or the resultant inflammation induces the production of substances which inhibit acid secretion directly or neutralise the acid once it has been secreted. Acute *H. pylori* induced gastritis is associated with hypochlorhydria, suggesting that *H. pylori* has the ability to inhibit acid secretion.¹⁸ Subsequent reports have identified a number of substances secreted in vitro by *H. pylori* that may inhibit acid secretion. These include a protein acid inhibitor¹⁹ and fatty acids which may inhibit the parietal cell H⁺-K⁺ ATPase directly.²⁰ However, it is not known whether these substances are present in sufficient quantity to produce a detectable antisecretory effect in

TABLE III Group median (95% CI) gastrin and pepsinogen (PG) I and PGII values before and four weeks after cure of *Helicobacter pylori* infection

	Before cure	After cure
Gastrin (pmol/l)	20.5 (18, 25)	17.0 (14, 19)
PGI (ng/ml)	87.1 (60, 118)	73.0 (55, 80)
PGII (ng/ml)	10.7 (7, 14)	7.0 (5, 11)
PGI/PGII	9.4 (5, 11)	8.8 (7, 12)

vivo. *H. pylori* infection may also reduce acid secretion indirectly by inducing an immune response which leads to the synthesis and production of interleukin 1 (IL-1), a potent inhibitor of gastric acid secretion.²¹ It is not possible to determine in the present study which, if any, of these mechanisms was responsible for the observed effect as there had been marked resolution of the gastritis as well as cure of the *H. pylori* infection during the four week interval before the pH-metry studies were repeated. In addition to potential antisecretory substances, *H. pylori* infection is also associated with the presence of acid neutralising compounds such as ammonia or other tertiary amines.^{22–24} We suggest that these buffer substances play the major role in the apparently greater antisecretory efficacy of omeprazole before cure of an *H. pylori* infection.

The present findings may have practical implications. Firstly, the results of all studies which have used pH-metry to correlate the degree of acid inhibition with the healing of peptic lesions should be re-evaluated.^{25–28} In the absence of stratification for *H. pylori* positive and *H. pylori* negative subjects, it is not possible to determine accurate therapeutic pH cut off points for the healing of particular acid-peptic diseases. Secondly, these data may explain why the average dose of an acid pump inhibitor necessary to produce healing is lower for *H. pylori* related diseases such as duodenal ulcer than for non-*H. pylori* related diseases such as reflux oesophagitis.²⁹ Finally, it remains to be determined whether the treatment of reflux oesophagitis is affected by cure of *H. pylori* gastritis.

TABLE II Group median H⁺ activity in mmol/l (95% CI) in the absence of omeprazole treatment (no omeprazole) and during omeprazole, before (*Helicobacter pylori* +ve) and after cure of *H. pylori* infection (H pylori -ve)

Time	No omeprazole		Omeprazole		Omeprazole induced fall in H ⁺	
	H pylori +ve (A)	H pylori -ve (B)	H pylori +ve (C)	H pylori -ve (D)	H pylori +ve (A-C)	H pylori -ve (B-D)
24 h	47.4 (40, 63)	63.0 (40, 100)	0.008 (10 ⁻⁴ , 0.06)	0.22 (0.03, 31)	47.3 (39, 63)	56.5 (38, 79)
M	24.5 (13, 50)	31.9 (18, 63)	0.008 (0.002, 0.02)	0.04 (0.006, 0.5)	24.2 (13, 50)	30.3 (17, 62)
D	63.0 (50, 79)	79.4 (63, 100)	0.004 (0.001, 0.04)	1.31 (0.01, 13)	63.0 (50, 79)	68.1 (46, 99)
N	44.9 (25, 79)	79.4 (39, 125)	0.001 (0.0002, 0.2)	0.5 (0.08, 25)	44.8 (25, 63)	66.5 (39, 99)
EN	63.1 (53, 101)	79.5 (63, 100)	0.6 (0.01, 8)	16.9 (0.6, 36)	62.8 (40, 79)	58.5 (34, 99)
LN	27.7 (0.06, 50)	68.0 (25, 125)	4 × 10 ⁻⁴ (10 ⁻⁵ , 0.003)	0.004 (3 × 10 ⁻⁴ , 32)	27.7 (0.05, 35)	49.4 (15, 99)

The omeprazole-induced fall in H⁺ activity is expressed as the difference between H⁺ activity in the absence of omeprazole and H⁺ activity during omeprazole treatment. 24 h: Entire recording, M: meal time, D: daytime, N: night-time, EN: early night-time, LN: late night-time.

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