

Effect of curing *Helicobacter pylori* infection on intragastric acidity during treatment with ranitidine in patients with duodenal ulcer

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Abstract

Background—In patients with duodenal ulcer cure of *Helicobacter pylori* infection resulted in a pronounced decrease in intragastric pH during treatment with omeprazole.

Aim—To test the hypothesis that treatment of *H pylori* adversely affects the pH response to ranitidine.

Patients—Eighteen patients with duodenal ulcer who were infected with *H pylori* were studied.

Methods—Twenty four hour pH recordings were performed during treatment with ranitidine (300 mg) at night before and four to six weeks after cure of *H pylori* infection. Presence of *H pylori* was assessed by a rapid urease test, culture, histology, and a ¹³C urea breath test. Also, the fasting gastrin concentrations were measured before and after treatment for *H pylori* infection.

Results—Cure of *H pylori* infection resulted in a considerable improvement in both antral and corpus gastritis and a decrease in fasting gastrin concentrations. As a result of the cure the night time intragastric pH during treatment with ranitidine decreased (median pH 6.8 v 5.4; p=0.007), whereas the acidity during the daytime was not affected.

Conclusions—In patients with duodenal ulcer the intragastric pH during treatment with ranitidine depends on *H pylori*. However, the loss of effectiveness in altering pH seems to be less pronounced than previously found with omeprazole.

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have presented evidence for such a neutralising system, other possible mechanisms come to mind. Firstly, it is well established that the severity of corpus gastritis increases during omeprazole treatment, interfering with acid secretion.^{5 6} Secondly, omeprazole is a prodrug which is activated in secreting parietal cells. If before the cure the proportion of secreting parietal cells was higher than after the cure, then less omeprazole would be activated after the cure. This would lead to a loss of effectiveness of the drug. One way to investigate such mechanisms is the use of a secretory inhibitor which is not activated in the parietal cells and to compare the results of such a drug with the omeprazole data. We therefore gave ranitidine to patients with duodenal ulcer before and after cure of *H pylori* infection.

Methods

STUDY POPULATION

Patients with an endoscopically established duodenal ulcer associated with *H pylori* infection and aged over 18 years were eligible for the study. Exclusion criteria were pretreatment with antisecretory drugs, sucralfate, bismuth compounds, or antibiotics during the previous four weeks, pregnancy or lactation, severe concomitant diseases, additional gastric ulcer or reflux oesophagitis, or a history of stomach surgery, except simple closure of a perforation, and a suspected lack of compliance (for example, alcohol or drug misuse). The study was conducted according to the Declaration of Helsinki. All patients gave written informed consent. The protocol was approved by the ethics committee of the University of Essen.

STUDY DESIGN

Before enrolment and four to six weeks after cessation of the anti-*H pylori* treatment, patients were investigated clinically and endoscopically. Four antral and four corpus biopsy specimens were assessed for *H pylori* using a rapid urease test (HUT test, Astra GmbH, Wedel, Germany), specific culture, histology (Warthin Starry stain), and the ¹³C urea breath test.

A 24 hour pH measurement was performed on day 8 of a course of ranitidine (300 mg at 2100) before the treatment for *H pylori* infection. Ranitidine treatment was followed by one week of *H pylori* treatment. Ulcer healing and cure of *H pylori* infection were

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We have previously shown that the pH response to omeprazole decreases after curing a *Helicobacter pylori* infection, both in healthy volunteers and in patients with a duodenal ulcer.^{1 2} This apparent loss of effectiveness is paralleled by the disappearance of acid neutralising ammonia produced by *H pylori*.^{3 4} It is conceivable that the neutralising effect of ammonia would become more evident if the H⁺ concentration in the gastric juice is low. This could explain why, after cure of the infection, the pH falls during omeprazole treatment but does not change in the spontaneously secreting stomach.¹ Although we

checked four to six weeks after cessation of all medication. A final pH recording was then performed on day 8 of a second course of ranitidine (300 mg at 2100).

TREATMENT FOR *HELICOBACTER PYLORI*

All patients were treated with omeprazole (40 mg twice daily), amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily) for one week.

24 HOUR PH-METRY

After an overnight fast, a glass pH electrode (Ingold 440-M3, Medical Instruments Corporation, Solothurn, Switzerland) was inserted transnasally and placed 5 cm below the cardia. The correct position was controlled fluoroscopically. The pH recordings were performed as previously described.¹ Patients took ranitidine (300 mg) at 2100.

ASSESSMENT OF *HELICOBACTER PYLORI* INFECTION

During each endoscopy four biopsy specimens were taken from both the lesser curvature of the proximal antrum and the greater curvature of the proximal body of the stomach. These were analysed by a rapid urease test, specific culture under microaerophilic conditions for three to five days, and histology using haematoxylin and eosin and Warthin and Starry stains to grade the gastritis and *H pylori* density.^{7,8} The urea breath test was performed with 75 mg ¹³C-labelled urea and orange juice as a test meal.⁹ An excess (>4%) was considered to be positive for *H pylori* infection. We defined cure of the *H pylori* infection as no evidence of persistent colonisation of the gastric mucosa by any method four to six weeks after cessation of the *H pylori* treatment.

GASTRIN ANALYSIS

Fasting gastrin concentrations were measured by radioimmunoassay (Diagnostic Products Corporation, Bad Nauheim, Germany) before and four to six weeks after the cure of the *H pylori* infection.

DATA ANALYSIS

The time intervals for the analysis of the pH recordings were predefined as follows: entire recording (0900–0900), combined postprandial periods (0930–1130, 1330–1530, 1930–2130), night time (2200–0600), and the remaining combined non-meal daytime period. Median pH values as well as the percentage of time spent at pH ≥ 3 were calculated for the entire recording and each of the time windows. Mean H⁺ concentrations (h \times mmol/l) were calculated from the raw pH values with "pack 3" software (Medical Instruments Corporation). All data are given as group median values with the interquartile range. Statistical comparisons were made using the Wilcoxon signed rank test for paired samples.

The gastritis scores and the urea breath test results before and after treatment were compared statistically with the two tailed Wilcoxon signed rank test for paired samples. Significance was considered at a 5% probability level.

Results

Eighteen patients (median age (range) 44 (23–75) years; 14 men; 11 current smokers) with relapsing duodenal ulcer disease associated with an *H pylori* infection were studied. The infection was cured in all patients as judged from negative bacterial findings by all four methods four to six weeks after cessation of treatment. All ulcers had healed at the time of follow up endoscopy. The elimination of *H pylori* infection was associated with a highly significant decrease in the total scores of both antral (11 (range 9–14) *v* 3 (1–5); *p*<0.0001) and body gastritis (5 (1–14) *v* 1 (1–2); *p*<0.0001) and the fasting gastrin concentrations (64.5 (34–158) pg/ml *v* 41.0 (19–84) pg/ml, *p*<0.0001).

During treatment with ranitidine the median intragastric pH was higher at night time before *H pylori* treatment than four to six weeks after the infection was cured, whereas the combined postprandial pH and the non-meal daytime pH remained unchanged (fig 1; table 1). There was only a trend towards a higher mean H⁺ activity after cure of *H pylori* infection (table 1). The time spent with pH values ≥ 3 and ≥ 4 was greater before *H pylori* treatment than after cure of the infection during the entire recording period and at night (table 1).

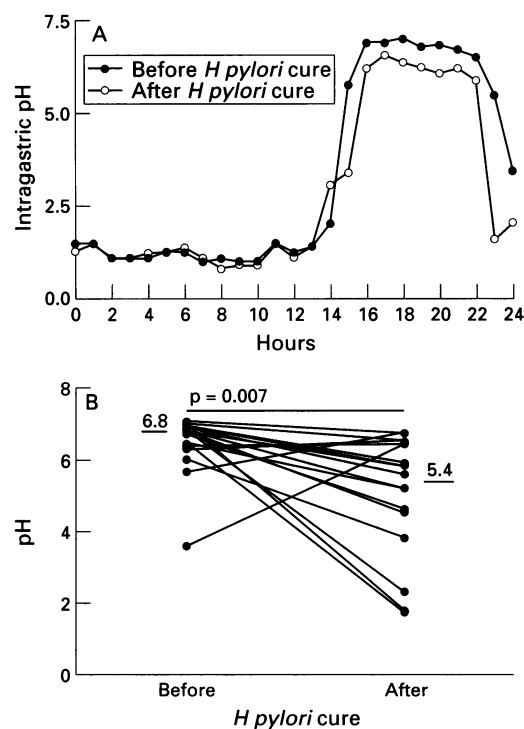


Figure 1: Median 24 hour pH curves (A) and individual night time intragastric pH (B) during treatment with 300 mg ranitidine (2100) before and after the elimination of *H pylori* infection in patients with duodenal ulcer. pH recordings started at 0900 hours.

TABLE 1 Intra-gastric acidity during treatment with ranitidine (300 mg) at night before and after treatment for H pylori infection in patients with duodenal ulcer

	Before treatment	After treatment	p Value
Median gastric H (IQR):			
24 hours	2.0 (1.8-2.1)	1.5 (1.3-2.1)	0.13
Daytime	1.3 (1.2-1.6)	1.2 (1.0-1.6)	0.26
Postprandial	1.4 (1.1-1.5)	1.2 (1.2-1.4)	0.18
Night time	6.8 (6.4-6.9)	5.4 (4.5-6.4)	0.007
Median H ⁺ (h \times mmol/l) (IQR):			
24 hours	44.3 (36.6-50.4)	58.4 (35.5-72.3)	0.14
Median time (%) >pH 3 (IQR):			
24 hours	42.8 (38.8-44.9)	32.0 (28.5-41.5)	0.02
Night time	84.1 (74.0-92.8)	74.2 (60.3-80.5)	0.04
Median time (%) >pH 4 (IQR):			
24 hours	38.8 (33.4-41.7)	27.3 (23.5-34.9)	0.006
Night time	79.4 (73.6-85.0)	62.8 (53.9-74.9)	0.04

IQR=Interquartile range.

Discussion

In the present study we have shown that ranitidine has a less pronounced effect on the gastric pH after cure of *H pylori* infection in patients with duodenal ulcer. This does not come as a surprise as it has been previously shown that *H pylori* generates ammonia,^{3,4} which may further increase the intra-gastric pH during treatment with antisecretory drugs. In healthy subjects the *H pylori* related increase in the effect of omeprazole is associated with ammonia production.¹⁰ The ammonia disappears with cure of the infection and this, in turn, could lead to an apparent loss of the effectiveness of secretory inhibitors.

The loss of effectiveness seems to be more pronounced in the case of omeprazole (median night time pH 6.4 before cure and 2.1 after cure¹) than in the case of ranitidine. Here, the median night time pH fell from 6.8 to 5.4. We cannot account for this difference between omeprazole and ranitidine but possible explanations come to mind. Firstly, the timing of drug administration differed between the studies and ranitidine acts rapidly but for a shorter time, whereas omeprazole irreversibly inactivates the proton pump but is circulating for a shorter time. Secondly, there could be a stronger transformation of omeprazole to the active sulphenamide in inflamed than in non-inflamed mucosa. It is known that cytokines such as interleukin-1 are expressed in inflamed mucosa¹¹⁻¹³ and may stimulate the release of secretagogues such as histamine, which in turn promote the transformation from resting parietal cells to active parietal cells.¹⁴ In addition, *H pylori* possesses N^α-histamine methyl-transferase activity and produces N^α-methyl histamine, which is a potent secretagogue and inhibitor of antral somatostatin release.¹⁵ This may accelerate the transformation of omeprazole into the active sulphenamide. In the case of ranitidine such activation does not take place and therefore ranitidine would be as effective before as after the cure. Thirdly, omeprazole, by contrast with ranitidine, also inhibited acid secretion during the day. This continuous inhibition is known to lead to more dense colonisation of the proximal part of the stomach with *H pylori*.^{5,16} The colonisation of the fundus and proximal corpus with *H pylori* determines the concentration of neutralising substances, such as ammonia, at the site of the electrode; the fall in neutralising substances

after cure would be more pronounced with omeprazole than with ranitidine. This could explain the apparent conservation of the effectiveness of ranitidine after cure. Fourthly, acid secretion depends on the severity of corpus gastritis,^{6,13} possibly mediated by cytokines such as interleukin-1.¹⁷⁻¹⁹ As the severity of corpus gastritis increases during treatment with omeprazole, this could account for the more pronounced augmentation of the pH raising effect in infected subjects. However, despite further improvement of the corpus gastritis during a one year follow up the pH response to omeprazole remained unchanged, both in healthy subjects and in patients with duodenal ulcer.^{20,21} Moreover, the severity of gastritis did not correlate with the magnitude of H⁺ concentration change induced by omeprazole.²¹ Therefore, it is less likely that changes in gastritis play a major part.

A weakness of our studies is that we cannot exclude differences in the intra-gastric pH in the spontaneously secreting stomach, neither between the study groups treated with omeprazole and ranitidine, nor within the study groups before and after the cure. However, we have shown that cure of *H pylori* infection does not affect the intra-gastric pH without treatment, both in healthy subjects and in patients with duodenal ulcer.^{1,21} Nevertheless, in future studies it will be necessary to give ranitidine in doses which also inhibit acid secretion during the day and omeprazole to the same patients before and after cure of *H pylori* infection, to make morphological assessments of resting and activated parietal cells before and after the cure, and to test other secretory inhibitors which are or are not given as prodrugs and activated in the parietal cell.

In conclusion, we have provided evidence that the effect of *H pylori* on the intra-gastric pH in response to ranitidine is small. The present study may have clinical implications. It will be important in the future to assess, for all secretory inhibitors, to what extent they lose their ability to raise intra-gastric pH in patients cured of *H pylori* infection. Whereas histamine antagonists are – compared with proton pump inhibitors – relatively weak secretory inhibitors, they may have the advantage of being comparably effective before and after cure of infection. It might be interesting to compare the effectiveness of ranitidine and omeprazole in patients with reflux oesophagitis after stratification for *H pylori*.

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