Eradicating *Helicobacter pylori* infection lowers gastrin mediated acid secretion by two thirds in patients with duodenal ulcer

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Abstract

Helicobacter pylori (*H pylori*) raises serum gastrin but it is unclear whether this stimulates increased acid secretion. Gastrin mediated acid secretion and plasma gastrin after the intravenous infusion of gastrin releasing peptide was studied in nine *H pylori* negative and nine *H pylori* positive healthy volunteers, and in 11 duodenal ulcer patients. Nine of the last group were re-examined one month after eradication of *H pylori*. The median acid output (mmol/h) to gastrin releasing peptide (40 pmol/kg/h) in the *H pylori* positive healthy volunteers was 15.1 (range 3.3-38.3), which was three times that of the *H pylori* negative healthy volunteers (median=5.5, range 1.0-9.0) ($p<0.02$). The median acid output in the duodenal ulcer patients with *H pylori* was 37 (range 8.5-57), which was > six times that of the *H pylori* negative healthy volunteers. Eradication of *H pylori* in the duodenal ulcer patients lowered their acid secretion by a median of 66% (range 30%-80%) ($p<0.01$) and to values equivalent to the *H pylori* positive healthy volunteers. The pepsin output in response to gastrin releasing peptide followed the same pattern as the acid output. The median plasma gastrin concentrations during gastrin releasing peptide were similar in the *H pylori* positive duodenal ulcer patients (150 ng/l, range 95-400) and *H pylori* positive healthy volunteers (129 ng/l, range 23-420) and both were appreciably higher than *H pylori* negative healthy volunteers (60 ng/l, range 28-135) ($p<0.005$ for each). Eradication of *H pylori* lowered the plasma gastrin in the duodenal ulcer patients to values equivalent to the *H pylori* negative healthy volunteers. These findings show a threefold increase in acid secretion in *H pylori* positive healthy volunteers that is explained by *H pylori* induced hypergastrinaemia and a sixfold increase in acid secretion in the duodenal ulcer patients that is explained by the combination of *H pylori* induced hypergastrinaemia and an exaggerated acid response to stimulation by gastrin. Eradicating *H pylori* lowers gastrin mediated acid secretion by 66% in duodenal ulcer patients as a result of the resolution of the hypergastrinaemia. Increased gastrin mediated acid secretion seems to be the key factor in the pathophysiology of duodenal ulceration and explains the role of *H pylori* infection in the disorder.

(Gut 1993; 34: 1060-1065)

pathogenesis of duodenal ulcer disease. It is present in >95% of duodenal ulcer patients and numerous studies have shown that eradicating the infection dramatically lowers the ulcer relapse rate.¹⁻⁴ The mechanism by which this infection, which predominantly affects the antral mucosa, predisposes to ulceration of the duodenum is unknown. Also, the reason why only a small proportion of subjects with this common infection develop duodenal ulceration is unclear.

We and others have shown that both duodenal ulcer patients and healthy volunteers with *H pylori* have increased basal and meal stimulated gastrin concentrations that fall after eradication of the infection.⁵⁻⁹ Though gastrin is recognised to be the main mediator of meal stimulated acid secretion,¹⁰ the effect of *H pylori* on acid secretion remains unclear. A major reason for this is the technical difficulty of reliably determining acid output in response to a meal. To overcome this problem we have measured gastrin mediated acid secretion after the intravenous infusion of gastrin releasing peptide. This stimulates the release of endogenous gastrin, which in turn stimulates acid secretion, and thus makes it possible to measure accurately the combined functional response of the antrum and body of the stomach. Gastrin releasing peptide like peptides also stimulate the release of cholecystokinin¹¹ and somatostatin¹² as well as other gastric inhibitory hormones¹¹ and in this way simulate the response to eating.

To elucidate the effect of *H pylori* on gastric function, we have examined basal and gastrin mediated acid secretion in healthy volunteers with and without *H pylori* and also in duodenal ulcer patients before and after eradicating the infection.

Patients and methods

Eleven *H pylori* positive patients (eight men) with chronic duodenal ulcer disease proved by endoscopy, nine *H pylori* positive healthy volunteers (seven men), and nine *H pylori* negative healthy volunteers (six men) were studied. The three groups were matched for age and body weight. There were eight smokers in the duodenal ulcer group and three in each of the other two groups. Duodenal ulcer patients were asked to stop any antisecretory treatment two weeks before the secretory studies. None of the healthy volunteers were taking any drug and none reported major gastrointestinal symptoms. *H pylori* infection was confirmed in the duodenal ulcer patients by microscopic examination of antral biopsy rapid urease test (CLO test) on antral biopsy, and by ¹⁴C urea breath test. In

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Helicobacter pylori (*H pylori*) infection is now recognised to be the main acquired factor in the

Figure 1: Basal plasma gastrin concentrations (A) and basal acid output (B) in healthy volunteers with and without *H. pylori*, and in duodenal ulcer patients before and after *H. pylori* eradication treatment. The before and after treatment values in the patient in whom the infection was not eradicated are joined by broken line. *Statistics applies only to the patients in whom the infection was eradicated.

healthy volunteers, *H. pylori* state was determined by the ^{14}C urea breath test.

SECRETORY STUDIES

All subjects reported at 0900 after a 12 hour fast. An orogastric tube (Anderson Inc, New York) was swallowed and its position in the dependent part of the stomach checked by the water recovery test. After emptying the stomach, intermittent suction was applied using an intermittent suction unit (Ohmeda, Columbia, USA)

that applies suction for 20 seconds in each 32 second cycle. Three 15 minute collections were obtained basally and at each of the following rates of intravenous infusion of gastrin releasing peptide: 10, 40, 100, and 200 pmol/kg/hr. Blood samples were collected every 15 minutes for gastrin determination and the plasma stored at -20°C . The secretory studies were all performed with the investigator blind to the subjects' *H. pylori* state.

Gastrin releasing peptide was purchased from Cambridge Research Biochemicals (Cheshire, England) in 0.5 mg aliquots. Each aliquot was made up into a stock solution by dissolving in sterile water. 0.1 ml of 50% acetic acid solution was added to stabilise the solution. Aliquots were stored at -80°C . For each study the aliquot was further diluted in 0.9% NaCl solution.

The volume and pH of each gastric juice collection was recorded and its hydrogen ion concentration measured by titration with 0.1 N NaOH to pH 7 using an autotitrator (Radiometer ETS 822). Gastric juice aliquots for pepsin measurement were centrifuged at 4°C . One ml of each aliquot was added to 0.3 ml of a Glycerol/HCl (10 mmol) solution 50/50 vol/vol. Samples were stored at -80°C before determination of pepsin activity by the method of Gray and Billings.¹³

Basal acid output was calculated by taking the mean of all three 15 minute samples before gastrin releasing peptide infusion. Acid and pepsin outputs for each gastrin releasing peptide infusion rate were calculated by taking the mean of the second and third 15 minute collections. Pepsin measurements were not performed in two of 10 duodenal ulcer patients after treatment.

Gastrin was measured by radioimmunoassay with antiserum R98¹⁴ that has a sensitivity of 5 ng/l. The basal gastrin value for each subject was measured by taking the mean of the three samples obtained before the start of gastrin releasing peptide infusion. The gastrin value at each infusion rate of gastrin releasing peptide was measured by taking the mean of the two values at 30 and 45 minutes of each infusion. To ensure accuracy, gastrin measurements were performed in the same assay batch. For this reason, gastrin results are not available in two of 11 duodenal ulcer patients before treatment and two of 10 duodenal ulcer patients after treatment who entered the study later.

ERADICATION OF *H. PYLORI*

After the above secretory studies, 10 duodenal ulcer patients were treated with tripotassium dicitratobismuthate 120 mg three times daily, metronidazole 400 mg three times daily, and amoxycillin 500 mg three times daily for three weeks. One month after completion of this treatment their ^{14}C -urea breath test was repeated to assess the *H. pylori* state. Their secretory studies were also repeated at this point.

STATISTICS

Statistical analysis of unpaired data was performed using the Mann-Whitney U test and of paired data using the Wilcoxon test. A p value of

Figure 2: Plasma gastrin concentrations (A) and acid output (B) during intravenous infusion of gastrin releasing peptide (40 pmol/kg/h). The before and after treatment values in the patient in whom the infection was not eradicated are joined by broken line. *Statistics applies only to the patients eradicated of *H. pylori*.

<0.05 was taken as significant. The study was approved by the Western Infirmary Ethical Committee.

Results

The repeat ^{14}C -urea breath test at one month after completion of the triple anti-*H. pylori* treatment showed that the infection had been eradicated in nine of 10 duodenal ulcer patients.

BASAL GASTRIN

The medium basal gastrin (ng/l) was increased by a similar extent in the *H. pylori* positive healthy volunteers (45, range 10–88) and *H. pylori* positive duodenal ulcer patients (47, range 22–175) compared with the *H. pylori* negative healthy controls (25, range 15–48) ($p < 0.005$ for both) (Fig 1A). After eradication of *H. pylori* the median serum gastrin in the duodenal ulcer patients fell to 28 (range 12–65) ($p < 0.02$ *v* before eradication), which was similar to the value in the *H. pylori* negative healthy volunteers.

BASAL ACID SECRETION

The median basal acid output (mmol/h) was similar in the *H. pylori* negative (1.3, range 0.7–4.6) and positive (2.2, range 1.0–13.3) healthy volunteers (Fig 1B). It was increased in the *H. pylori* positive duodenal ulcer patients (6.6, range 3.1–23.2), however, compared with both the *H. pylori* negative healthy volunteers ($p < 0.005$) and *H. pylori* positive healthy volunteers ($p < 0.05$). Eradication of *H. pylori* lowered the median basal acid output in the nine duodenal ulcer patients to 3.6 (range 1.2–8.4) ($p < 0.01$ *v* before eradication), representing a median reduction of 50% (20%–80%). The basal acid output in the one duodenal ulcer subject in whom *H. pylori* infection was not eradicated was similar before (3.7) and after (4.8) the triple treatment.

GASTRIN RESPONSE TO GASTRIN RELEASING PEPTIDE

At the gastrin releasing peptide infusion rate of 40 pmol/kg/h the median plasma gastrin concentration (ng/l) was increased to a similar value in the *H. pylori* positive healthy volunteers (129, range 23–420) and *H. pylori* positive duodenal ulcer patients (150, range 94–400) and each was higher than that of the *H. pylori* negative healthy volunteers (60, range 28–135) ($p < 0.005$ for each) (Fig 2A). After eradication of *H. pylori* the median gastrin concentration in response to gastrin releasing peptide 40 pmol/kg/h in the nine duodenal ulcer patients fell to 68 (range 23–115) ($p < 0.02$ *v* before eradication), which was similar to the value in the *H. pylori* negative healthy volunteers.

Though the gastrin concentration increased with increasing gastrin releasing peptide infusion rates, the four groups of subjects showed the same pattern of response at each infusion rate (Fig 3A). The statistical differences between the groups were the same at each infusion rate as that seen at 40 pmol/kg/h. We chose to present the results of the individual data points for the 40 pmol/kg/h gastrin releasing peptide rate as the gastrin concentrations stimulated by this are closest to those seen after a meal.

ACID RESPONSE TO GASTRIN RELEASING PEPTIDE

At gastrin releasing peptide 40 pmol/kg/h the median acid output (mmol/h) in the *H. pylori* positive healthy volunteers (15.1, range 3.3–38.3) was about three times that of the *H. pylori* negative healthy volunteers (5.5, range

Figure 3: Median plasma gastrin concentration (A) and median acid output (B) in response to increasing infusion rates of gastrin releasing peptide in the different groups examined.

1.0–9.0) ($p < 0.02$) (Fig 2B). At this infusion rate the median acid output in the *H. pylori* positive duodenal ulcer patients was 37 (range 8.5–57), which was about twice that of the *H. pylori* positive healthy volunteers ($p < 0.02$) and six times that of the *H. pylori* negative healthy volunteers ($p < 0.001$). After eradication of *H. pylori* the acid output in the nine duodenal ulcer patients fell by a median of 66% (range 30%–80%) to a median value of 13.7 mmol/h

(range 6.2–24) ($p < 0.01$) and thus became similar to that of the *H. pylori* positive healthy volunteers but remained higher than the *H. pylori* negative healthy volunteers ($p < 0.005$). Gastrin mediated acid secretion did not fall in the one patient whose infection was not eradicated (Fig 2B).

The acid response to gastrin releasing peptide was again consistent in the four groups at each of the infusion rates of gastrin releasing peptide studied (Fig 3B).

PEPSIN RESPONSE TO GASTRIN RELEASING PEPTIDE
The pepsin response to gastrin releasing peptide showed the same pattern as the acid response at each infusion rate of gastrin releasing peptide. The differences between the groups, however, were most evident at the gastrin releasing peptide infusion rate of 100 pmol/kg/h (Fig 4).

In response to gastrin releasing peptide 100 pmol/kg/h the median pepsin output (units/h) in the *H. pylori* positive healthy volunteers (18, 15–43) was higher than the *H. pylori* negative volunteers (12, 6–25) ($p < 0.02$). The median pepsin output in the *H. pylori* positive duodenal ulcer patients (29, 19–60) was higher than both the *H. pylori* positive ($p < 0.005$) and negative ($p < 0.001$) healthy volunteers. Eradication of *H. pylori* in the duodenal ulcer patients lowered their pepsin output by a median of 55% to 17 units/h (11–55) ($p < 0.03$) making them similar to the *H. pylori* positive healthy volunteers.

Discussion

This study shows that chronic *H. pylori* infection is accompanied by appreciably increased gastric acid output in both healthy volunteers and duodenal ulcer patients. It also shows that the infection increases both basal and stimulated acid secretion.

In the healthy volunteers with *H. pylori* both their basal gastrin and gastrin response to gastrin releasing peptide were increased compared with the *H. pylori* negative healthy volunteers. The two–threefold increase in gastrin response to gastrin releasing peptide in the *H. pylori* positive healthy volunteers is consistent with their previously reported two–threefold increased gastrin response to a meal.^{6,9} The design of this study allowed us to show that this increased gastrin response is accompanied by a concomitant threefold increase in acid secretion. This is consistent with the recent studies showing that the increased gastrin concentration in *H. pylori* infection is due to a rise in the biologically active G17 form of the hormone.^{15,16}

The duodenal ulcer patients with *H. pylori* infection resembled the *H. pylori* positive healthy volunteers with respect to their serum gastrin concentrations both basally and at each infusion rate of gastrin releasing peptide. This is consistent with our previous finding that the gastrin response to a meal is exaggerated by a similar extent in *H. pylori* positive duodenal ulcer patients and *H. pylori* positive healthy volunteers.⁶ The *H. pylori* positive duodenal ulcer patients and *H. pylori* positive healthy volunteers differed, however, with respect to gastrin mediated acid secretion, which was increased sixfold

Figure 4: Pepsin output during intravenous infusion of gastrin releasing peptide (100 pmol/kg/h) in healthy volunteers with and without *H pylori* and in duodenal ulcer patients before and after *H pylori* eradication treatment. The before and after treatment values in the patient in whom the infection was not eradicated are joined by broken line. *Statistics applies only to the patients in whom the infection was eradicated.

in the first but only threefold in the second when compared with *H pylori* negative healthy volunteers. The fact that the duodenal ulcer patients secreted more than twice as much acid as the *H pylori* positive healthy volunteers despite having equivalent gastrin concentrations shows that the duodenal ulcer patients have an exaggerated acid response to stimulation by gastrin. This finding is consistent with the previous studies showing that duodenal ulcer patients have an increased sensitivity to pentagastrin¹⁷⁻¹⁹ as well as to endogenous gastrin released in response to a peptone meal.²⁰

Our data, therefore, show that subjects with *H pylori* infection who develop duodenal ulceration have two disturbances of gastric function: (1) increased release of gastrin by the antral mucosa and (2) an exaggerated acid response to stimulation by gastrin. It is this dual defect that causes their considerable sixfold increase in gastrin mediated acid secretion. The increased antral gastrin release is explained by the *H pylori* infection though the mechanism by which the infection stimulates gastrin release is unknown. It may be secondary to the recent findings of reduced somatostatin concentrations in the presence of *H pylori* infection.^{21,22} The exaggerated acid response to gastrin can be explained by the increased parietal cell mass present in duodenal ulcer patients.²³ The increased parietal cell mass may be due to the longterm trophic effects of *H pylori* induced hypergastrinaemia on the oxyntic mucosa,^{24,25} due to smoking,²⁶ represent the genetic factor in duodenal ulcer, or be due to any combination of these.

After eradication of *H pylori* infection in the duodenal ulcer patients their gastrin fell to the same value as the *H pylori* negative healthy volunteers and this was accompanied by a 66% fall in their gastrin mediated acid secretion after gastrin releasing peptide. This brought acid secretion in the duodenal ulcer patients into the range of the *H pylori* positive healthy volunteers but it did not fall to the values of *H pylori* negative healthy volunteers. This is explained by the fact that eradicating *H pylori* resolved the increased acid secretion caused by the increased antral gastrin release but did not resolve that caused by their exaggerated acid response to gastrin. The second finding is consistent with our previous study showing that the response to pentagastrin stimulation in duodenal ulcer patients is not changed after eradication of *H pylori*.²⁷ The fact that the exaggerated acid response to gastrin did not resolve after eradication of *H pylori* does not exclude it being due to trophic effects of *H pylori* induced hypergastrinaemia on the oxyntic mucosa. The half life of the parietal cell is 23 days in rats²⁸ and presumably much longer in man and therefore it could take many months for resolution of an increased parietal cell mass.

Increased basal and nocturnal acid output are also important features of duodenal ulcer disease^{29,30} and in this study the median basal acid output of the *H pylori* positive duodenal ulcer patients was five times that of the *H pylori* negative healthy volunteers. After eradication of *H pylori* in the duodenal ulcer patients both their basal acid output and basal gastrin fell by 50%. Though gastrin is considered to be the main mediator of food stimulated acid secretion,¹⁰ its role in the regulation of basal acid output is unclear. The fact that the fall in basal gastrin with eradication of *H pylori* in the duodenal ulcer patients was accompanied by a fall in basal acid secretion suggests that the increased basal gastrin was stimulating gastric secretion in the absence of food. Further evidence of this is the fact that the value of gastrin that increased acid secretion after gastrin releasing peptide in the *H pylori* negative healthy volunteers was equivalent to the basal gastrin value in the *H pylori* positive duodenal ulcer patients. Though basal gastrin was increased to a similar extent in *H pylori* positive healthy volunteers and *H pylori* positive duodenal ulcer patients the first did not have a significantly increased basal acid output. This may be explained by the fact that the increased basal acid output in duodenal ulcer patients was due to their combination of increased basal gastrin and exaggerated acid response to gastrin. It is probable that the increased basal gastrin is also stimulating increased basal acid secretion in the *H pylori* positive healthy volunteers, which will become discernible after lowering of the gastrin by eradicating the infection.

In addition to increased acid secretion, duodenal ulcer patients are known to have increased pepsin secretion³¹ and it is the increased exposure to this combination of acid and pepsin that is likely to be injurious to the duodenal mucosa. In our studies pepsin output correlated closely with acid output. The beneficial effect of eradicating *H pylori* in duodenal ulcer patients is therefore

explained by the consequent lowering of gastric acid and pepsin secretion to the values present in non-ulcer (*H. pylori* positive) subjects.

The finding in this study that gastrin mediated acid secretion is so appreciably increased (six-fold) in duodenal ulcer patients compared with true normal subjects (*H. pylori* negative healthy volunteers) implies that it is likely to be the key factor in the pathophysiology of duodenal ulcer disease. The effect of *H. pylori* on gastrin mediated acid secretion provides a scientific explanation for the role of the infection in the pathogenesis of duodenal ulceration.

Because of the fact that permanent reduction of acid secretion can be achieved by a single course of *H. pylori* eradication treatment, there seems little justification to continue to treat duodenal ulcer patients with repeated courses of expensive acid suppressive agents.

This work was supported by grants from the Biomedical Research Committee of the Scottish Home and Health Department and the Research Support Group of the Greater Glasgow Health Board. The authors gratefully acknowledge the assistance of the staff of the Department of Nuclear Medicine, Western Infirmary; the statistical advice of Miss Catherine Howie; the technical assistance of Mrs Devina Fillmore, Sister Liz Spence, and Mrs Jennifer Harwood and the invaluable secretarial assistance of Mrs Dorothy Ronney.

This work was presented at the 1992 Autumn Meeting of the British Society of Gastroenterology and appeared as an abstract in *Gut*.

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