

Acid secretion and sensitivity to gastrin in patients with duodenal ulcer: effect of eradication of *Helicobacter pylori*

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Abstract

The effect of ulcer healing with eradication of *Helicobacter pylori* (*H pylori*) on gastric function was investigated in nine patients with duodenal ulcer disease. One month after eradication there were significant reductions in both basal plasma gastrin concentration, from a median (range) of 19 (1-22) to 6 (2-15) pmol/l ($p < 0.05$), and of basal acid secretion from 8.3 (2.4-24) to 2.6 (1.4-8.1) mM H^+ /h, ($p < 0.01$). The peak acid secretion rate was unchanged from 37 (16-59) to 37 (21-59) mM H^+ /h. After treatment there was no change in the parietal cell sensitivity to stepped infusions of gastrin heptadecapeptide: the median concentration of gastrin required for 50% of maximal acid secretion (EC_{50}) was 41 (14.8-126) before and 33 (23-125) pmol/l after eradication of *H pylori*. The metabolic clearance rate of gastrin was also unaffected by the eradication of *H pylori*. Thus eradication of *H pylori* infection from patients with active duodenal ulcers is accompanied by falls in both basal gastrin release and basal acid secretion without a change in the parietal cell sensitivity to gastrin. Cyclical changes in *H pylori* infection may cause the variations in basal acid secretion that are seen in duodenal ulcer disease.

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Despite the strong epidemiological and clinical evidence implicating the bacterium *Helicobacter pylori* (*H pylori*) in the pathogenesis of chronic duodenal ulcer disease,¹ the way that the organism promotes recurrence of ulcers remains unclear.

The discovery that *H pylori* increases plasma gastrin concentrations raised the possibility that *H pylori* may be responsible for the known abnormalities of gastric acid secretion that have been described in patients with duodenal ulcers. These include high basal and peak acid outputs, a high ratio of basal to peak acid secretion, increased meal stimulated acid output, and impairment of the normal inhibition of gastrin release and acid secretion by luminal acid.²⁻⁵

Helicobacter pylori increases plasma gastrin concentrations by 50% to 100% and values fall to normal after the organism has been eradicated.⁶⁻¹⁰ Despite this reduction in plasma gastrin, no consistent changes in rates of acid secretion have been documented after eradication treatment. This has led to the suggestion that *H pylori* infection might decrease the sensitivity of parietal cells to gastrin,¹¹ but other evidence did not support this view. Chittajallu *et al* were

unable to detect a change in the response to stepped infusions of pentagastrin on eradication of *H pylori* from patients with duodenal ulcer disease, although circulating concentrations of pentagastrin were not measured.¹² Furthermore, earlier studies of patients with duodenal ulcer disease, who were presumably mostly infected, showed their parietal cells to be, if anything more sensitive to gastrin than those of controls,^{13,14} although it was not known whether the controls were infected with *H pylori*.

We therefore studied acid secretory responses to gastrin in a series of patients with duodenal ulcer disease before and after treatment to eradicate *H pylori*. Because the hypergastrinaemia in *H pylori* infection is predominantly due to an increase in the antral gastrin form, gastrin heptadecapeptide (G17),^{15,16} we infused G17 intravenously and determined the effect of eradication of *H pylori* on acid secretion, parietal cell sensitivity to gastrin, and the metabolic clearance of G17.

Methods

PATIENTS AND TREATMENT

The study was approved by the local ethics committee. Eleven patients were recruited from our outpatient clinic and informed consent was obtained. The patients, eight men, had a median age of 34 (range 21-76) years; five were smokers, each smoking 20 cigarettes per day. As entry criteria they all had active uncomplicated duodenal ulceration at endoscopy and *H pylori* infection diagnosed by a biopsy urease test, histology, and bacterial culture. At least two of these tests were positive in all the patients studied at entry. None had any complicating medical condition or previous history of gastric surgery, or had taken antibiotics or bismuth preparations in the previous six months. Apart from antacids none of the patients had taken any medical treatment during the 14 days before their initial endoscopy.

Acid secretory responses to gastrin (see later) were measured within five days of endoscopy. Patients were then treated with 120 mg tripotassium dicitratobismuthate (DeNol, Brocades, Weybridge, Surrey, UK) four times daily for one month, 400 mg metronidazole three times daily, and 500 mg tetracycline four times daily taken concurrently for the first two weeks of treatment. Four weeks after the end of treatment endoscopy was repeated and biopsies were taken. The acid secretory tests were repeated within five days of the second endoscopy.

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G17 DOSE-RESPONSE STUDIES

Patients attended the clinical investigation unit at 9:00 am after fasting overnight. Indwelling venous cannulae were inserted into the right forearm for infusion of G17 and into the left forearm for blood sampling. Gastric acid secretion was measured by aspiration as described by Baron.³ Briefly, a nasogastric tube was passed, resting juice was aspirated, and the position of the tube was checked by water recovery. The tube used was a multifenestrated sump tube with a second channel for infusing phenol red into the proximal stomach and a third lumen for equilibration of intragastric and atmospheric pressure. The patient remained semirecumbent throughout. Gastric contents were constantly aspirated under 20 mm Hg negative pressure (Air Shields, Hatboro, Pa, USA) and the patency of the tube was ensured by the manual insufflation of 20 ml air every five minutes.

The G17 (Gastrin I Human; Sigma, Poole, Dorset, UK) made up in 0.15M saline containing 1% albumin was infused continuously by an infusion pump (Vickers Medical, Basingstoke, Hants, UK) at doses of 0, 11, 33, 100, and 300 pmol/kg/h, each for a 30 minute period. The largest dose produces maximal stimulation of acid secretion.^{14,17} Gastric acid was collected continuously on to ice and the acid output during each 15 minute period was measured by titration to pH 7 with 0.1M NaOH. The rate of acid secretion was calculated with correction for pyloric losses and duodenogastric reflux by phenol red recovery and sodium measurement respectively.³ Median (range) gastric juice recoveries were 90 (74–100)% before and 85 (78–100)% after treatment. Basal acid output per hour was calculated by doubling the acid output during the 30 minutes of infusion of saline only. Other acid outputs were calculated by multiplying the acid output during the second 15 minutes of each infusion period by four. Blood samples were taken at the end of each infusion period for gastrin assay.

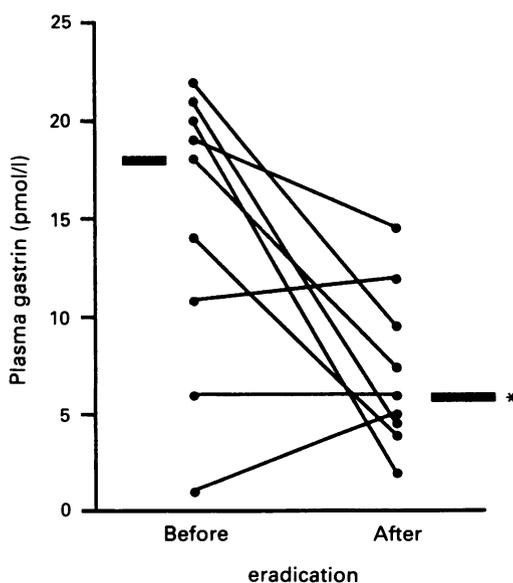


Figure 1: Changes in basal plasma gastrin concentration in nine patients with duodenal ulcers after eradication of *H. pylori* with tripotassium dicitratobismuthate, tetracycline, and metronidazole. Bars represent median values. * $p < 0.05$.

MEASUREMENT OF GASTRIN

Blood was collected into chilled tubes containing EDTA and the plasma was separated promptly and frozen at -20°C . Plasma gastrin concentration was measured by radioimmunoassay with antibody G179 provided by Professor Bloom.¹⁸ All samples were assayed in duplicate and in the same assay. Individual dose-response curves were then plotted.

STATISTICAL ANALYSIS

The data were analysed with an Arcus 2 statistical package (Medical Computing, Aughton, W. Lancs, UK). Wilcoxon's rank sum test was used to compare differences before and after treatment and the results are expressed as medians (ranges) and 95% confidence intervals (95% CIs). A p value < 0.05 was considered to signify statistical significance.

Results

CLINICAL

At repeat endoscopy ulcers had healed in 10 of the 11 patients. The patient with a duodenal ulcer at the end of treatment (man aged 31 years) had positive urease, histology, and bacteriology for *H. pylori* when retested and a woman aged 66 years still had a positive urease test after treatment. These patients were excluded from further analysis. In the remaining nine patients *H. pylori* was successfully eradicated, and endoscopic findings were normal. Data from these nine patients were then analysed further.

BASAL PLASMA GASTRIN

Basal plasma gastrin concentrations fell significantly after the eradication of *H. pylori* (Fig 1). The median basal plasma gastrin concentration before treatment was 19 (range 1–22, 95% CI 9–20) pmol/l compared with 6 (2–15, 95% CI 4–11) pmol/l after ($p < 0.05$).

BASAL AND PEAK ACID SECRETION RATES

Figure 2 shows that after eradication of *H. pylori* there was a reduction of basal acid output in eight patients and no change in one patient. The median basal acid output fell significantly from 8.3 (2.4–24, 95% CI 4.4–16) to 2.6 (1.4–8.1, 95% CI 2.0–6.0) mM H^+ /hour ($p < 0.01$). The peak acid output was unchanged, from 37 (16–59, 95% CI 31–45) to 37 (21–59, 95% CI 27–45) mM H^+ /hour after treatment.

PARIETAL CELL SENSITIVITY TO GASTRIN

Figure 3 shows that for the nine patients as a group, there was a linear relation between the mean plasma gastrin during infusion of G17 plotted on a log scale and the mean acid output at each of the G17 doses. This relation was linear both before and after treatment, with correlation coefficients of 0.99 ($p < 0.001$, 95% CI 0.89–1.00) and 0.98 ($p < 0.005$, 95% CI 0.71–1.00) respectively. The only differences between the two lines is that after treatment there was a lower mean

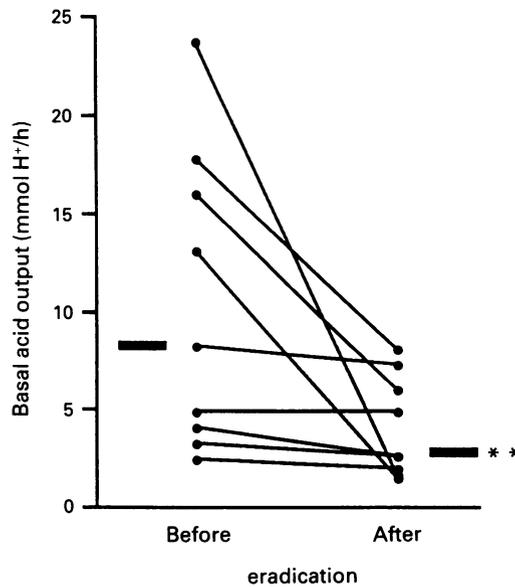


Figure 2: Basal acid output before and after eradication of *H pylori*. Bars represent median values. ** $p < 0.01$.

plasma gastrin concentration and a lower mean acid secretion rate under basal conditions. Consequently, the mean concentration of gastrin necessary to produce half maximal acid secretion (EC_{50}) was identical, both before and after eradication of *H pylori*.

Individual dose-response curves for each patient were also plotted. From these the EC_{50} for each patient – rather than the group as a whole – was determined, both before and after eradication of *H pylori*. In the nine patients in whom *H pylori* was eradicated, the median correlation coefficient of the individual regression plot of log dose against response was 0.93 (0.85–0.96) before and 0.94 (0.89–0.99) after treatment. There was no significant difference in the EC_{50} after the eradication of *H pylori*. The median EC_{50} was 41 (14.8–126) pmol/l before and 33 (23–125) pmol/l after eradication.

The basal-subtracted EC_{50} – the concentration of gastrin necessary to increase acid secretion from basal to half maximal acid secretion – has been advocated by some workers to be a more appropriate index of parietal cell sensitivity.¹⁹ This is because this analysis excludes the effect of changes in basal acid secretion, which is thought to be independent of gastrin.^{20,21} We therefore also plotted individual dose-response curves of log plasma gastrin against the basal-subtracted acid output. The correlation coefficients for these plots were 0.94 (0.85–0.96) and 0.94 (0.88–0.99) before and after treatment respectively. In the nine patients in whom *H pylori* was successfully eradicated the median basal-subtracted EC_{50} fell significantly, from 104 (18–171, 95% CI 53–150) to 48 (26–136, 95% CI 34–103) pmol/l ($p < 0.05$).

METABOLIC CLEARANCE RATES OF G17

By comparing the infused G17 dose with the plasma gastrin response the metabolic clearance rate of G17 can be calculated by two different methods as described by Blair *et al*.²² The clearance rate can be calculated by the reciprocal

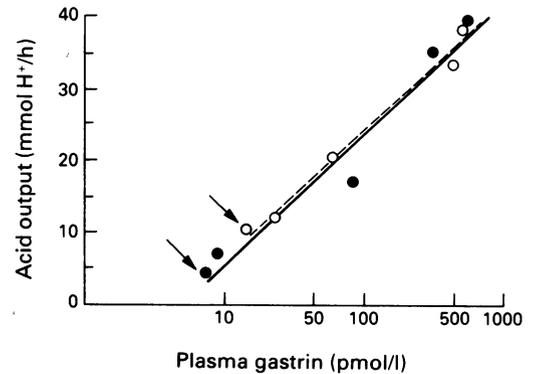


Figure 3: Relation between mean plasma gastrin concentration and acid output during the last 15 minute period of each G17 infusion. Mean values for the nine patients at each dose of G17 before eradication of *H pylori* are indicated by open circles joined by the dashed line and after eradication by dark circles and bold line. The points indicated by arrows represent mean values under basal conditions.

of the slope of the regression line between G17 dose and plasma gastrin and by the plateau principle at an infusion rate of G17 of 300 pmol/kg/hour. The metabolic clearance rate of G17 was 8 (6–93) before and 8 (6–76) ml/kg.min after treatment when calculated by the first method and 9 (6–74) and 8 (6–62) ml/kg.min respectively by the second method. Therefore the clearance of G17 was not altered by the eradication of *H pylori*.

Discussion

Our current results confirm that treatment which both heals duodenal ulcers and eradicates *H pylori* significantly decreases basal plasma gastrin concentrations. We have also shown for the first time such treatment also decreases basal gastric acid secretion significantly. Thus *H pylori* infection combined with active ulceration may cause the increased basal acid secretion seen in duodenal ulcer disease.

Several previous studies have shown that eradication of *H pylori*, with or without ulcer healing, produces a fall in fasting plasma gastrin concentrations.^{6–10} Abolition of the exaggerated gastrin release is probably due to an increase in the synthesis of somatostatin in the antral mucosa.^{23–25} Despite a fall in the basal plasma gastrin concentration, however, it has not been shown previously that eradication of *H pylori* can significantly decrease the basal acid output. Two previous studies, one by ourselves in patients with duodenal ulcers²⁶ and another by Mountbriand *et al* in dyspeptic patients²⁷ showed no significant change in basal acid output after anti-*H pylori* treatment. In both studies the patients were retested within a week of ending treatment, however, so that in some cases infection may have persisted.²⁸ When six patients with duodenal ulcers in whom *H pylori* had been eradicated were retested after 12 months, we found that the median basal acid output fell by about 40%,²⁹ although the change was not significant. Fullarton *et al* noted a fall of about the same degree, one month after eradicating *H pylori* from eight patients with inactive duodenal ulcer disease, but again the change was not statistically significant.³⁰ We also found the basal acid output

to be significantly greater in patients with duodenal ulcers and with *H pylori* than in patients with duodenal ulcers without this infection.⁶ It is difficult to deduce the physiological effect of *H pylori* on basal secretion from this and other studies in which patients do not act as their own controls, because other differences between the groups might affect acid secretion. For example, *H pylori* is implicated in the pathogenesis of atrophic gastritis,³¹ which may have led to decreased acid secretion through loss of parietal cells in groups of chronically infected subjects in some studies.³² The fall in basal acid secretion found may not necessarily be due to the eradication of *H pylori*. Achord noted that the basal acid output decreased after healing of an ulcer by drugs that do not eradicate *H pylori*,³³ implying that the ulcer crater is itself associated with increased basal acid secretion. Further studies will be necessary to determine which factor – the ulcer crater or *H pylori* – is responsible for the increased basal acid output.

Our present findings are consistent with the generally accepted view that peak acid output reflects the parietal cell mass and is not altered by eradication of *H pylori*.^{10 27 29 30} The main purpose of our present study was to determine whether chronic infection with *H pylori* alters the sensitivity of the parietal cells to gastrin. This was suggested by the relative lack of change in rates of acid secretion and intragastric acidity on eradication of *H pylori* despite substantial falls in circulating gastrin concentrations,^{6–10} and by the suppression of acid secretion produced by *H pylori* on first infection.³⁴

We measured circulating gastrin to determine the concentrations of gastrin required to produce half maximal acid secretion. There has been debate as to whether this should be calculated with or without subtraction of basal acid secretion. It is widely held that the increased basal acid secretion in patients with duodenal ulcer disease is determined by vagal drive rather than circulating gastrin.^{20 21} This is the rationale for determining the basal subtracted EC₅₀ in some previous studies.^{13 14 17 19} We found that basal-subtracted EC₅₀ does fall significantly on eradication of *H pylori*, suggesting that the infection initially present did indeed decrease the sensitivity of parietal cells to gastrin. The effect of eradication of *H pylori* on basal gastrin and acid secretion is more consistent with the idea that circulating gastrin is responsible for driving basal acid secretion in patients with duodenal ulcer, because the fall in basal gastrin concentration on eradication was accompanied by a proportional fall in basal acid secretion. Therefore the EC₅₀, rather than the derived basal-subtracted EC₅₀, is likely to be the most appropriate measure of parietal cell sensitivity and the EC₅₀ did not change after healing with eradication of *H pylori*. It is now clear that the change in basal-subtracted EC₅₀ on eradication plus healing is only a mathematical consequence of the fall in gastrin driven basal acid secretion. This is best appreciated when the mean acid output is plotted against mean plasma gastrin concentration for each G17 infusion (Fig 3); the two lines are identical when exogenous gastrin is infused. These graphs are similar to those obtained by

Hirschowitz *et al*¹⁷ and by Blair *et al*²² who compared G17 dose-response curves in patients with ulcers and control subjects, after normalising for differences in peak acid secretion rates; the only difference between the two groups of patients was under basal conditions.

Blair *et al* found that the metabolic clearance rate of G17 was lower in patients with duodenal ulcers than in controls.¹⁹ Our results show no change in the clearance of G17 on eradication of *H pylori*. The results that we obtained were similar to the results in their duodenal ulcer group so that the results of Blair *et al* cannot be explained by the presence of *H pylori*.

Our present results show that healing of duodenal ulcers with a regime that also eradicates *H pylori* produces a fall in basal acid secretion that may be due to the concomitant fall in basal plasma gastrin concentration. Increased basal acid secretion has been implicated in duodenal ulcerogenesis and correction of this abnormality may contribute to the prolonged remissions of this disease seen after eradication of *H pylori*.

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