Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with *Helicobacter pylori*

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Abstract

An ELISA test determined serologically that eight of 95 apparently healthy men (aged 19–26 years) had an asymptomatic infection with *Helicobacter pylori* at the time of simultaneous measurement of 24 hour intragastric acidity and 24 hour plasma gastrin concentration. There was no significant difference in the median integrated 24 hour intragastric acidity between the *H. pylori* positive and *H. pylori* negative subjects (688 and 842 mmol/l; p=0.271, respectively), whereas the median integrated 24 hour plasma gastrin concentration was significantly higher in the *H pylori* positive than in the *H pylori* negative subjects (389 and 198 pmol/l; p<0.001). Long-term hypergastrinaemia, associated with persistent *H pylori* infection, could be a cause of the increased parietal cell mass that is considered characteristic of duodenal ulcer patients.

There is increasing interest concerning the role of *H pylori* in the pathogenesis of peptic ulcer disease and gastritis, with evidence to support the hypothesis that eradication of *H pylori* infection in the gastric mucosa decreases the chance of ulcer relapse. There are five reports describing *H pylori* associated gastric hyperchlorhydria and four reporting normal acidity, but duodenal ulceration is usually associated with hyperacidity. One study has shown that the mean pentagastrin stimulated acid output was significantly higher in 25 *H pylori* positive duodenal ulcer patients compared with six *H pylori* negative patients.

The aim of this retrospective analysis was to determine serologically, using a sensitive and specific ELISA test, which of 95 apparently healthy subjects were asymptomatically infected with *H pylori* at the time of measurement of their 24 hour intragastric acidity profile and 24 hour plasma gastrin concentration.

Methods

**SUBJECTS**

Retrospective data on simultaneous 24 hour intragastric acidity and 24 hour plasma gastrin concentration from 95 apparently healthy male subjects (age 19–26 years) were gathered from research records at the Royal Free Hospital. All the subjects had taken part in clinical pharmacology studies during the preceding three years. The data used for this analysis were derived from the placebo arms of these studies, some of which have been published.

**ETHICAL APPROVAL**

Ethical approval was given by the Royal Free Hospital's Ethics Committee, and written consent was obtained from every subject. None of the subjects had a history of peptic ulcer disease, gastritis or upper gastrointestinal pathology. Routine physical examination, haematology and biochemistry profiles were normal.

**INTRAGASTRIC ACIDITY**

The subjects were studied using a standard protocol. They were admitted to a research ward when fasting. A 10 French gauge salem sump nasogastric tube (Argyle Medical) was positioned in the stomach. Aliquots (5–10 ml) of intragastric contents were aspirated hourly throughout the study, using disposable sterile bladder syringes, and the pH of each aliquot measured immediately to the nearest 0.01 pH unit by means of a glass electrode and digital pH meter (Radiometer, Copenhagen). The electrode was calibrated with standard buffers (pH 7.00, 4.01, and 1.09; Radiometer, Copenhagen) before and halfway through each batch of samples. Gastric aspirates were never replaced in the stomach to avoid cross infection between subjects.

**PLASMA GASTRIN CONCENTRATION**

Every hour from 0800 hours to 2400 hours, and two hourly between 2400 hours and 0800 hours, blood was taken through a venous cannula for the assay of plasma gastrin concentration. The blood was collected in lithium heparin tubes which already contained 0.2 ml aprotinin (Trasylol, Bayer). They were immediately centrifuged, the plasma transferred to plastic tubes and stored at −20°C. All the plasma samples from each subject were analysed for gastrin in one batch by radioimmunoassay, using antibody GAS 179 in Professor Stephen Bloom’s laboratory at the Hammersmith Hospital, London.

The subjects were fully ambulant around the ward during each study. The food and environmental conditions were identical for all the studies. The following standard meals were served: breakfast, coffee, lunch, tea, dinner and a bedtime snack at 0915 hours, 1115 hours, 1315 hours, 1615 hours, 1915 hours, and 2215 hours respectively.

**IgG ANTIBODIES TO H PYLORI**

Duplicate plasma samples from every study had been stored at −20°C. One sample from each subject was sent for serological analysis on dry
ice to the Veterans Administration Medical Center, Houston, Texas. Each sample was analysed using a sensitive (98-7%) and specific (100%) ELISA test for IgG-directed antibodies against high molecular weight cell-associated proteins (HM-CAP) of _H pylori_. Wells of 96 well microtitre plates (Linbro, Scientific Co, Hamden, CT) were coated with purified HM-CAP diluted with phosphate buffered saline to approximately 7 μg/ml. After 18–24 hours at 37-5°C excess plastic protein binding sites were blocked with 1% bovine serum albumin in phosphate buffered saline, and sera diluted 1:50 and 1:100 added in duplicated. Optimal dilutions of alkaline phosphatase conjugated antihuman IgG (Southern Biotechnology, Birmingham, Alabama) were used as the detector using standard ELISA methods. Each plate included HM-CAP-ELISA positive and negative control sera. Serum dilution of 1:50 or 1:100 and a 'cut off' optical density of 0-200 gave good discrimination between _H pylori_ infected and uninfected individuals.

**STANDARD ANALYSIS**

Twenty-four hour profiles of intragastric acidity and plasma gastrin concentration were obtained for the 95 subjects. Median values were calculated for every hourly measurement. The integrated area under the time concentration curve for each profile was calculated by the trapezoid rule. Integrated 24 hour acidity was expressed as mmol/h/l and integrated 24 hour plasma gastrin concentration as pmol/h/l. One way analysis of variance (Kruskal-Wallis test) was performed on the median hourly intragastric acidity and plasma gastrin profiles. Differences between the profiles of 24 hour integrated intragastric acidity and plasma gastrin concentration were compared using the Mann-Whitney U test. The correlation between 24 hour integrated intragastric acidity and 24 hour integrated plasma gastrin concentration was tested using the Spearman rank correlation test. All statistical calculations used the Oxstat program (Microsoft Corporation).

**Results**

Eight of the 95 men were found to be anti-HM-CAP positive for _H pylori_, signifying active infection at the time of the 24 hour study, despite apparent good health.

The median 24 hour integrated intragastric acidity for the _H pylori_ negative subjects was 842 mmol/h/l (range 274–1393 mmol/h/l), and 688 mmol/h/l (range 527–1405 mmol/h/l) for the positive; this difference is not significant (p=0-079, Mann Whitney U test). Figure 1 shows the hourly intragastric acidity (95% confidence limits) of the 87 _H pylori_ negative subjects compared with the 24 hour intragastric acidity of the eight _H pylori_ positive subjects (95% confidence limits), showing that there is no difference in the acidity profiles between the two groups (0-3<p<0-2, Kruskal-Wallis analysis of variance). The median integrated 24 hour plasma gastrin concentration for the _H pylori_ negative subjects was 198 pmol/h/l (range 87–918 pmol/h/l); the median value for the _H pylori_ positive subjects was significantly higher (381 pmol/h/l; range 329–2254 pmol/h/l; p=0-001).

Figure 2 shows the hourly plasma gastrin concentration (95% confidence limits) for the 88 _H pylori_ negative subjects, compared with the profile for the eight _H pylori_ positive subjects (median; 95% confidence limits). The latter profile is significantly higher than that of the _H pylori_ negative subjects (p<0-001, Kruskal-Wallis analysis of variance).

Figure 3 shows that there is a significant inverse correlation between integrated 24 hour intragastric acidity and integrated 24 hour plasma gastrin concentration in the 88 _H pylori_ negative healthy subjects (Rs=−0-379, p<0-001; Spearman rank correlation test). The eight _H pylori_ positive patients had a raised integrated 24 hour plasma gastrin concentration.
in the presence of low but normal 24 hour intragastric acidity.

Discussion
This study shows that asymptomatic apparently healthy *H pylori* infected young individuals have an exaggeration of the normal inverse relationship between acidity and plasma gastrin with a low, but normal, 24 hour intragastric acidity and a significantly raised 24 hour plasma gastrin concentration.

Of the five reports describing gastric hypoacidity associated with *H pylori* infection, two describe an acute loss of gastric acid secretion observed during serial experiments in man,11 one describes a negative significant correlation between the total number of mucosa related bacteria and either basal acid output or pentagastrin-stimulated maximal acid output; the two remaining papers describe either a raised fasting gastric pH or occasional decreased acidity during endoscopy.10 11 Normal gastric acidity was found during the endoscopy of 102 dyspeptics (38% *H pylori* positive) in Finland;14 maximal acid output, and fasting or postprandial plasma gastrin concentrations, were similar in *H pylori* positive and negative duodenal ulcer patients from Hong Kong;15 Brady et al could not detect a constant relationship between *H pylori* and either gastric acid secretion or fasting serum gastrin concentration – 24 hour pH monitoring was similar in seven normal subjects, 10 patients with *H pylori* negative active chronic gastritis, and 12 patients with *H pylori* positive chronic gastritis.16 Levi et al reported that the basal and peak acid

Figure 2: Plasma gastrin concentration (95% confidence limits) in 87 *H pylori* negative healthy subjects compared with plasma gastrin concentration in eight *H pylori* positive subjects (median; 95% confidence limits).
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output to pentagastrin were higher in H pylori positive duodenal ulcer patients compared with H pylori negative patients (7-3 and 5-5, and 44-2 and 30-7, respectively).18 This study also showed that the H pylori infected patients had a significantly greater postprandial release of gastrin, compared with the non-infected patients.

It is probable that the inappropriately high plasma gastrin concentrations in the eight symptomatic H pylori positive individuals identified in this study are the result of an effect of the bacterium on the antral G-cell population. Alternatively, gastrin may be released to stimulate gastric acid secretion, thereby overcoming hypochlorhydria caused by earlier bacterial damage to the mucosa.

The apparently healthy H pylori positive subjects identified in this study might in later years develop duodenal ulceration. As spontaneous eradication of H pylori seems unusual, the continuing hypergastrinaemia could induce an increase in the parietal cell mass, to produce the hyperacidity characteristic of duodenal ulcer disease.22-26 One report has suggested that maximal acid output in duodenal ulcer patients increases gradually three to nine years after the onset of dyspepsia.27

If H pylori is the cause of inappropriate hypergastrinaemia22-28 and the gastric acid hypersecretion of duodenal ulceration, it may be anticipated that eradication of the organism will be followed by a decrease in gastrin release and possibly a gradual decrease in the gastric acid secretory capacity of the stomach. This sequence of events could be tested by prospective clinical studies before and after eradication of H pylori: one study has shown a 32% fall in the fasting plasma gastrin concentration associated with clearance at one month of H pylori by amoxycillin and tinidazole in a group of 30 children.29

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