

PAPERS

Eradicating *Helicobacter pylori* reduces hypergastrinaemia during long term omeprazole treatment

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Abstract

Background—Both proton pump inhibitor drug treatment and *Helicobacter pylori* infection cause hypergastrinaemia in man.

Aims—To determine whether eradicating *H pylori* is a means of reducing hypergastrinaemia during subsequent proton pump inhibitor treatment.

Methods—Patients with *H pylori* were randomised to treatment with either anti-*H pylori* or symptomatic treatment. One month later, all received four weeks treatment with omeprazole 40 mg/day for one month followed by 20 mg/day for six months. Serum gastrin concentrations were measured before and following each treatment.

Results—In the patients randomised to anti-*H pylori* treatment, eradication of the infection lowered median fasting gastrin by 48% and meal stimulated gastrin by 46%. When gastrin concentrations one month following anti-*H pylori*/symptomatic treatment were used as baseline, omeprazole treatment produced a similar percentage increase in serum gastrin in the *H pylori* infected and *H pylori* eradicated patients. Consequently, in the patients in which *H pylori* was not eradicated, median fasting gastrin concentration was 38 ng/l (range 26–86) at initial presentation and increased to 64 ng/l (range 29–271) after seven months omeprazole, representing a median increase of 68% ($p < 0.005$). In contrast, in the patients randomised to *H pylori* eradication, median fasting gastrin at initial presentation was 54 ng/l (range 17–226) and was unchanged after seven months omeprazole at 38 ng/l (range 17–95).

Conclusion—Eradicating *H pylori* is a means of reducing the rise in gastrin during subsequent long term omeprazole treatment. In view of the potential deleterious effects of hypergastrinaemia it may be appropriate to render patients *H pylori* negative prior to commencing long term proton pump inhibitor treatment.

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Keywords: hypergastrinaemia; *Helicobacter pylori*; omeprazole

Hypergastrinaemia is a well recognised side effect of treatment with proton pump inhibitor drugs.¹ This occurs due to the marked suppression of gastric acid secretion and thus removal of the acid mediated inhibition of gastrin release.^{2,3} The clinical significance of such hypergastrinaemia in patients requiring long term proton pump inhibitor treatment is unclear.

In rats, long term omeprazole treatment is associated with argyrophil cell hyperplasia within the oxyntic mucosa⁴⁻⁶ and the development of gastric carcinoid tumours in up to 30% of female animals.^{7,8} These changes in the rats have been shown to be a consequence of the drug induced hypergastrinaemia.⁹ In man, long term treatment with omeprazole also results in argyrophil cell hyperplasia which correlates with the degree of hypergastrinaemia.^{10,11} Gastrin also exerts trophic effects on gastric and colonic mucosa and on certain carcinoma cell lines derived from these tissues.^{12,13} The possible role of hypergastrinaemia in the development and growth of certain gastrointestinal tumours is uncertain but continues to attract research interest.^{14,15} Due to the uncertainty about the clinical significance of long term hypergastrinaemia in man, it would seem prudent to minimise the disruption of gastrin physiology induced by proton pump inhibitor drugs if possible.

Another common cause of chronic hypergastrinaemia in humans is *H pylori* infection,¹⁶ which is present in about 50% of the adult population.¹⁷ There is little information concerning the influence of *H pylori* status on the gastrin response to proton pump inhibitor treatment. In the present study, we have examined this and in particular assessed whether eradicating *H pylori* infection prior to commencing omeprazole treatment could be a means of reducing the hypergastrinaemia during subsequent proton pump inhibitor treatment.

Materials and methods

PATIENTS

Thirty three patients (22 males, mean age 40 years, range 22–60) with endoscopically confirmed peptic ulcer disease and/or oesophagitis entered the randomised study. Each of the patients had evidence of *H pylori* infection confirmed by microscopy of antral biopsy specimens.

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STUDY DESIGN

On entry to the study all patients had their serum gastrin concentration assessed while fasting and in response to a standardised meal. A ^{14}C urea breath test was performed simultaneously. Any acid inhibitory drugs were stopped at least four weeks prior to this assessment. Following this they were randomised to receive either *H pylori* eradication treatment consisting of three weeks treatment with tripotassium dicitratobismuthate 120 g three times daily, metronidazole 400 mg three times daily, and amoxicillin 250 mg three times daily plus Gastrocote (alginic acid, aluminium hydroxide, magnesium trisilicate, and sodium bicarbonate; Boehringer Mannheim, Livingstone, UK) as required for symptoms, or Gastrocote alone. Four weeks after completing this treatment all patients had repeat serum gastrin studies and ^{14}C urea breath test and endoscopic examination.

Subjects then received four weeks treatment with omeprazole 40 mg/day followed by six months treatment with omeprazole 20 mg/day. Omeprazole was taken before breakfast. During the final week of the seven month course of omeprazole, the serum gastrin measurements and endoscopic examination were repeated. The proton pump inhibitor was then stopped and patients maintained if required on Gastrocote for four weeks before having a further ^{14}C urea breath test.

COMBINED ^{14}C UREA BREATH TEST AND GASTRIN ASSESSMENT

Patients reported between 09.00 and 10.00 hours following an overnight fast. Subjects cleaned their teeth and an intravenous cannula was inserted. Three 20 ml venous blood samples were obtained at 15 minute intervals for fasting gastrin determination. A breath sample was collected for baseline ^{14}C CO_2 determination. The subjects then drank, over five minutes, 250 ml Ensure Plus (Abbott Labs Ltd, Maidenhead, UK) which contains 1.25 MJ/200 ml, 12.5 g protein, 40 g carbohydrate, 10 g fats, and vitamins (including vitamin A, vitamin D, vitamin K, vitamin C, vitamin E, folic acid, and vitamins B₁, B₂, and B₆) plus elements of sodium, potassium, and calcium.

Immediately following this they drank 100 ml water containing 0.4 MBq ^{14}C urea. Additional 20 ml blood samples for serum gastrin were obtained at 15 minute intervals for 90 minutes. A further breath sample for $^{14}\text{CO}_2$ determination was obtained at 20, 40, and 100 minutes following administration of the ^{14}C CO_2 .

When the combined gastrin/breath tests were performed at the end of the omeprazole treatment periods, the omeprazole medication was taken that morning two hours prior to commencing the test.

ENDOSCOPIC EXAMINATION

During each endoscopic examination three biopsy specimens were taken from the antrum of the stomach for histology, rapid urease test¹⁸ (CLO test, Delta West Pty Ltd, Bentley, Australia) for *H pylori*, and culture for *H pylori*.

COMPLIANCE

Compliance with the omeprazole treatment schedule was assessed by performing capsule counts at each visit. Compliance was considered unacceptable if more than 25% of the total tablets were not taken over the treatment period.

ANALYSES

Serum gastrin concentration was measured by radioimmunoassay using antibody R98 which detects G17 and G34 with similar affinity.¹⁹ Fasting gastrin was calculated as the median of the three samples obtained at 15 minute intervals prior to commencing the meal. The meal stimulated gastrin was calculated as the median of the three samples obtained at 15, 30, and 45 minutes. This time was chosen as it represented the time showing the maximal gastrin response to the meal.

Gastric biopsy specimens were transported to the laboratory in 0.9% sterile saline and cultured within four hours.²⁰ The biopsy specimens were homogenised and inoculated on to a blood agar base no. 2 (Oxoid) agar plate²¹ containing 10% vol/vol horse blood and Skirrows selective supplement (Oxoid). The plates were incubated for 72 hours at 37°C in a microaerophilic atmosphere (BBL Campypak). Typical colonies which were oxidase and urease positive were identified as *H pylori*.

Antral mucosal biopsy specimens for histological assessment were fixed in formalin, embedded in paraffin wax, and 4 µm sections obtained. Sections at three levels were stained with haematoxylin and eosin for assessment of the presence or absence of gastritis. One section was stained using cresyl fast violet for assessment of *H pylori* colonisation.

STATISTICS

The statistical significance of changes following the various treatments within each group was assessed by the Wilcoxon paired samples ranking test. The statistical significance of differing responses between the *H pylori* eradicated and non-eradicated groups was assessed by the Wilcoxon rank sum test.

ETHICS

The study was approved by the West Glasgow Hospitals University NHS Trust Ethics Committee.

Results

Of the thirty three patients randomised, poor compliance with the omeprazole treatment or failure to attend for examination resulted in 12 patients being excluded from the final analysis. Of the 21 patients who completed the study, 10 were randomised to *H pylori* eradication treatment and nine of them were *H pylori* negative when reassessed four weeks following discontinuation of the treatment. Each of those nine had a 20 minute ^{14}C urea breath test value of less than 14 kg percentage dose/mmol $\text{CO}_2 \times 100$, a negative antral CLO test, no *H pylori* on microscopy, and negative culture of antral biopsy specimens. The one patient who was still positive had a 20 minute ^{14}C urea breath

test value of more than 362, positive antral CLO test, and positive microscopy and culture of antral biopsy specimens. Of the 11 subjects who completed the study and received only symptomatic treatment, all remained positive for *H pylori* one month post-treatment by each of the above tests.

ENDOSCOPIC FINDINGS

Of the nine patients in whom *H pylori* was subsequently eradicated, their endoscopic diagnoses on initial presentation included duodenal ulceration in five, oesophagitis in three, and duodenal ulceration plus oesophagitis in one. The only endoscopic abnormality in those patients at one month after triple therapy was mild oesophagitis in one patient. One patient in whom the triple therapy failed to eradicate *H pylori*, had duodenal ulceration but showed complete healing one month after triple therapy.

Of the 11 patients who received symptomatic treatment, endoscopic findings at initial presentation included duodenal ulceration in seven, prepyloric ulceration in two, oesophagitis in one, and duodenal ulceration plus oesophagitis in one. On reassessment, after two months symptomatic treatment alone, endoscopic examination showed duodenal ulceration in four, oesophagitis in two, prepyloric ulceration in two, and duodenal ulcer and gastritis in one; two patients showed no persisting abnormality.

Endoscopic examination was normal in each of the subjects reassessed after six months treatment with omeprazole 20 mg per day.

H PYLORI ASSESSMENT DURING OMEPRAZOLE TREATMENT

Of the nine patients in whom *H pylori* was successfully eradicated when examined one month after triple therapy, all had negative antral CLO tests, negative antral culture, and negative histology for *H pylori* when reassessed after seven months of omeprazole treatment.

Of the 12 patients who were *H pylori* positive after symptomatic or triple therapy, three had both negative antral CLO test and no evidence of *H pylori* on microscopy of antral biopsy specimens; two of these patients showed resolution of antral gastritis after seven months of omeprazole therapy. One further patient had no evidence of *H pylori* on antral microscopy. Seven of them were negative for *H pylori* on culture.

The ¹⁴C urea breath tests performed four weeks after completing the seven months of omeprazole treatment were negative in all those initially eradicated of the infection by triple therapy and positive in all those who had unsuccessful triple therapy or symptomatic treatment.

SERUM GASTRIN

On initial presentation prior to treatment with triple/symptomatic therapy, the patients in whom *H pylori* was subsequently eradicated had similar fasting (median 54 ng/l, range 17–226) and meal stimulated serum gastrin concentrations (median 114 ng/l, range 31–286) compared with the patients in whom the infection was not subsequently eradicated

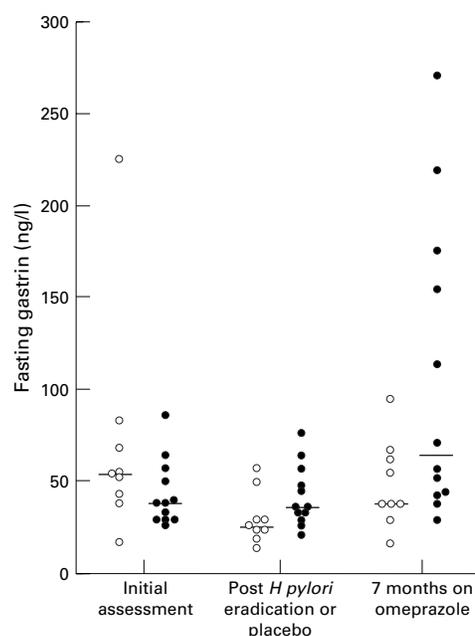


Figure 1 Fasting serum gastrin concentrations on initial assessment when all subjects were *H pylori* positive, following randomisation to *H pylori* eradication or no eradication, and following subsequent seven months' treatment with omeprazole. Subjects who had *H pylori* eradicated prior to omeprazole are represented by open circles.

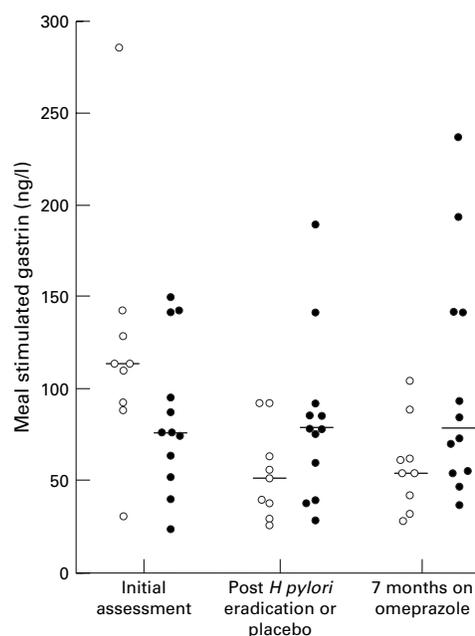


Figure 2 Meal stimulated gastrin concentrations on initial assessment when all subjects were *H pylori* positive, following randomisation to *H pylori* eradication or no eradication, and following subsequent seven months' treatment with omeprazole. Subjects who had *H pylori* eradicated prior to omeprazole are represented by open circles.

(fasting median 38 ng/l, range 26–86; meal stimulated median 76 ng/l, range 24–150) (figs 1 and 2).

On reassessment at one month following failed triple therapy or symptomatic treatment there was no change in fasting or meal stimulated gastrin concentrations. In contrast, in the patients in whom *H pylori* was eradicated

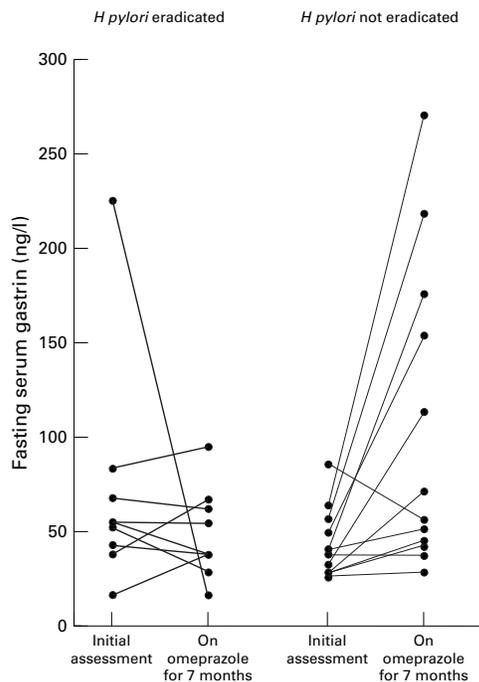


Figure 3 Fasting serum gastrin concentrations at initial assessment and after seven months omeprazole in subjects in whom *H pylori* was and was not eradicated prior to commencing proton pump inhibitor treatment.

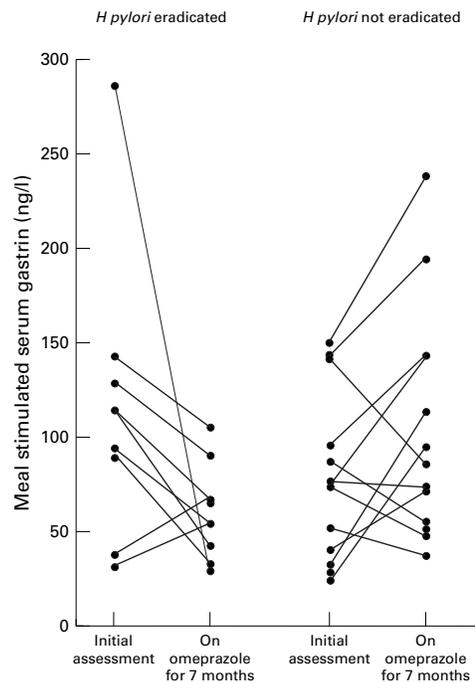


Figure 4 Meal stimulated gastrin concentrations at initial assessment and after seven months omeprazole in subjects in whom *H pylori* was and was not eradicated prior to commencing proton pump inhibitor treatment.

cated, median fasting gastrin fell by 48% and meal stimulated gastrin by 46% ($p < 0.01$ for each) (figs 1 and 2).

In the patients in whom *H pylori* was not eradicated, median fasting gastrin at the end of seven months of omeprazole treatment was 56% higher than that immediately prior to omeprazole ($p < 0.005$) although median meal stimulated gastrin was only 1% higher (not statistically significant). Likewise, in the patients in whom *H pylori* was eradicated, median fasting gastrin at the end of the seven months of omeprazole was 56% higher than that immediately prior to starting omeprazole, although meal stimulated gastrin was only 4% higher (not statistically significant) (figs 1 and 2).

Compared with values at initial assessment (before anti-*H pylori* or symptomatic treatment), the median fasting gastrin concentration in those in whom *H pylori* was not eradicated was increased by 26 ng/l after seven months of omeprazole treatment ($p < 0.005$), representing an increase of 68%. In contrast, in patients in whom *H pylori* was eradicated before omeprazole treatment, the fasting gastrin concentration was decreased by 12 ng/l after seven months omeprazole; this was not significantly different and represented a fall of 22% (fig 3). In the patients in whom *H pylori* was not eradicated, median postprandial gastrin concentration after seven months omeprazole was similar to that on initial presentation. In the patients in whom *H pylori* was eradicated before omeprazole treatment, median postprandial gastrin concentration after seven months omeprazole was 59 ng/l lower than on initial presentation, representing a 52% decrease ($p < 0.05$) (fig 4).

Using the initial values (before anti-*H pylori*/symptomatic therapy) as baseline, the change in gastrin following the seven month course of omeprazole was different in those in whom *H pylori* was subsequently eradicated than in those in whom it was not eradicated with respect to both fasting gastrin ($p < 0.03$) and meal stimulated gastrin ($p < 0.01$) (figs 5 and 6).

Median fasting gastrin during omeprazole treatment was higher in those in whom *H pylori*

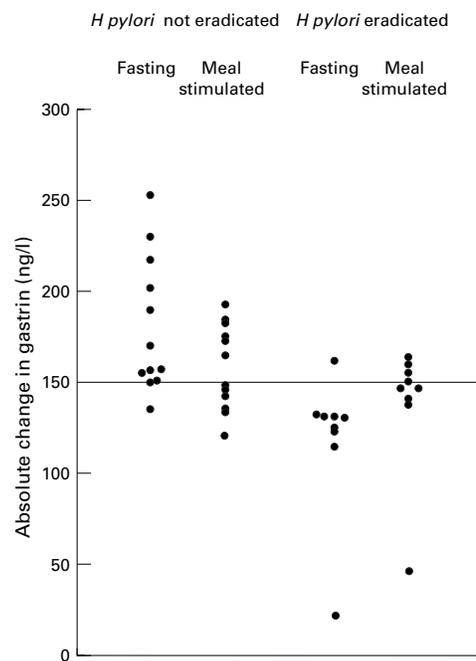


Figure 5 Absolute change in serum gastrin concentrations between initial assessment and end of seven months omeprazole in subjects in whom *H pylori* was or was not eradicated prior to proton pump inhibitor treatment.

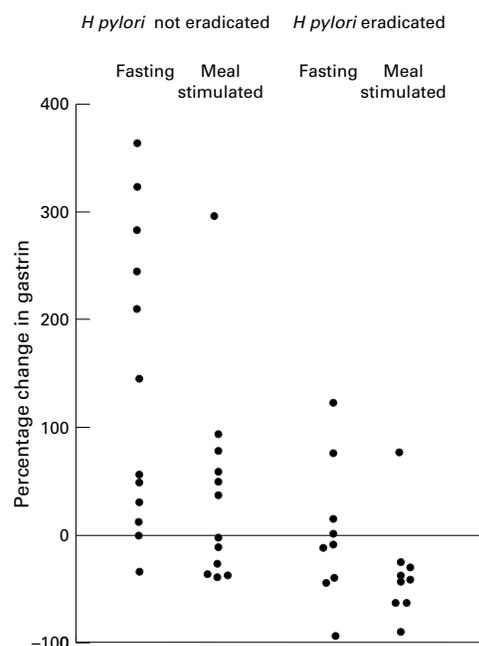


Figure 6 Percentage change in serum gastrin concentrations at initial assessment and after seven months omeprazole in subjects in whom *H pylori* was and was not eradicated prior to commencing proton pump inhibitor treatment.

was not eradicated (64 ng/l, range 29–271) than in those in whom it was eradicated (38 ng/l, range 17–95) though this did not quite reach conventional statistical significance ($p < 0.08$). Likewise, the median meal stimulated gastrin during omeprazole treatment was higher in those in whom *H pylori* was not eradicated (79 ng/l, range 38–238) than in those in whom it was eradicated (55 ng/l, range 29–105), though again this did not quite reach statistical significance ($p < 0.08$).

Discussion

Proton pump inhibitor drugs and *H pylori* infection are both important causes of hypergastrinaemia.^{1,16} Due to the high prevalence of *H pylori* infection, a considerable proportion of subjects prescribed long term proton pump inhibitor treatment will be *H pylori* positive and there is therefore interest in the combined effects of the two on serum gastrin. The present study indicates that *H pylori* infection and proton pump inhibitor treatment have an additive effect on serum gastrin. This observation is consistent with our previous study with five days treatment with another proton pump inhibitor, pantoprazole.²² Our findings are also consistent with studies prior to the recognition of *H pylori* which noted that subjects with higher pretreatment gastrin, probably related to *H pylori* infection, also had higher values during omeprazole treatment.^{23,24} The present study also shows that eradicating *H pylori* infection is a means of reducing the rise in gastrin during subsequent proton pump inhibitor treatment.

Though both *H pylori* infection and proton pump inhibitor treatment cause hypergastrinaemia, the present study indicates that they differ in the degree to which they raise fasting

and meal stimulated gastrin concentrations. Eradication of *H pylori* infection was associated with a more profound fall in meal stimulated than fasting gastrin concentrations and this is consistent with many previous studies showing that the infection predominantly increases meal stimulated gastrin concentrations.²⁵ In contrast, in the present study, proton pump inhibitor treatment resulted in a greater percentage rise in fasting gastrin concentrations than meal stimulated concentrations and this was apparent in both *H pylori* positive and *H pylori* eradicated subjects. The relative efficacy of omeprazole and *H pylori* in raising meal stimulated gastrin concentrations explains how the combination of omeprazole plus *H pylori* eradication actually lowered meal stimulated gastrin, the *H pylori* eradication gastrin lowering effect being greater than the omeprazole gastrin elevating effect. The reason for omeprazole having a more marked effect on fasting than meal stimulated gastrin may be explained by the difference in fasting and fed intragastric pH. Fasting pH is usually considerably less than 3 and at this intragastric acidity gastrin release is inhibited.²⁶ Omeprazole usually raises fasting pH above 4, thus disinhibiting gastrin release.²⁷ Following a meal intragastric pH may already be above pH 4 due to the buffering effect of the food and thus gastrin release will already be disinhibited. Consequently, any additional increase in pH due to omeprazole may have relatively little effect on the postprandial gastrin level.

The resultant effect on gastrin of proton pump inhibitor treatment plus *H pylori* infection will depend on the mechanism by which each independently produces hypergastrinaemia. As stated above, the former is thought to cause hypergastrinaemia by removing the inhibition of gastrin release exerted by low intragastric pH.^{2,3} Hypergastrinaemia associated with *H pylori* infection is thought to be secondary to depletion of antral somatostatin which exerts paracrine inhibitory control on gastrin release by the antral G cells.^{28–30} Somatostatin is largely responsible for mediating the inhibition of gastrin release exerted by low intragastric acid pH³¹ and impaired inhibition of gastrin release at low pH occurs in the presence of *H pylori* infection.³² Thus, both *H pylori* infection and acid inhibitory therapy are thought to cause hypergastrinaemia by disrupting the inhibition of gastrin release normally exerted by gastric acid. If that is the case, it might be expected that acid inhibitory treatment would result in a greater percentage increase in gastrin in *H pylori* negative subjects who start with their gastrin normally suppressed by acid than in *H pylori* positive subjects in whom the infection has already disinhibited gastrin release. However, in our present study we found that the percentage increase in gastrin during omeprazole treatment was at least as great in the presence versus absence of *H pylori* infection. This disparity may be explained by additional factors influencing the combined effect of *H pylori* plus omeprazole on serum gastrin.

The first of these additional factors is the recent observation that the degree of elevation of intragastric pH caused by omeprazole is dependent on *H pylori* status. Verdu *et al*^{33,34} observed that omeprazole 20 mg/day raised daytime pH from 1.3 to 5.4 in *H pylori* positive subjects but from 1.4 to only 2.9 in *H pylori* negative subjects. Likewise, it raised night-time pH from 1.1 to 4.7 in *H pylori* positive subjects, but from 1.1 to only 1.9 in *H pylori* negative subjects. The mechanism by which *H pylori* infection accentuates the antacid effects of omeprazole is unclear. However, it is known that there is an increase in severity of corpus gastritis³⁵ in *H pylori* positive subjects during omeprazole treatment and this may impair the acid secreting capacity of the oxyntic mucosa. Whatever its mechanism, this accentuated pH elevation produced by omeprazole in *H pylori* positive subjects will result in more complete disinhibition of gastrin release.

Recent studies indicate that there is progression of corpus atrophy during long term proton pump inhibitor treatment in *H pylori* positive subjects which does not occur in uninfected subjects.^{36,37} The development of atrophy during longer term omeprazole treatment will further reduce intragastric acidity and consequently further increase gastrin concentrations in *H pylori* positive subjects.

Another factor influencing the combined effect of omeprazole and *H pylori* on gastrin is the observation that omeprazole treatment reduces the density of the infection present in the gastrin producing antral region of the stomach.^{35,38,39} In the present study, *H pylori* infection was cleared from the antral mucosa by omeprazole in approximately one third of subjects. This suppression of *H pylori* in the antral region by omeprazole will tend to reduce hypergastrinaemia by reducing the *H pylori* induced hypergastrinaemia. This may explain the variations in degree of hypergastrinaemia seen in *H pylori* positive subjects during treatment with omeprazole.

Although the interacting mechanisms involved in the combined effects of *H pylori* and omeprazole on gastrin are complex, the present study shows that eradicating *H pylori* is a means of reducing the rise in gastrin during subsequent omeprazole treatment. In view of the uncertainty about some of the possible long term sequelae of hypergastrinaemia in man, it may be appropriate to screen for *H pylori* prior to commencing long term proton pump inhibitory treatment and eradicate it when present. A similar policy has recently been advocated in order to prevent the development of corpus atrophy during long term proton pump inhibitory treatment.^{36,37} Whether such a policy will also reduce the clinical efficacy of the proton pump inhibitor due to reducing its pH elevating effect is unknown.

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