Behaviour of acid secretion, gastrin release, serum pepsinogen I, and gastric emptying of liquids over six months from eradication of *Helicobacter pylori* in duodenal ulcer patients. A controlled study.

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Abstract

The behaviour of basal and stimulated acid secretion, gastrin release, serum pepsinogen I, and gastric emptying of liquids was studied in 19 consecutive patients with *Helicobacter pylori* positive duodenal ulcer, over a follow up period of six months. Eleven patients were studied before and at three and six months after eradication with lansoprazole plus amoxicillin and tinidazole (case group), whereas the remainder, with persistent *H pylori* infection, were studied before and after three and six months from ulcer healing, thus constituting the control group. In the case group, three months after eradication, fasting serum pepsinogen I fell from (mean (SEM)) 91.9 (6.9) (pretreatment) to 72.2 (5.1) ng/l and the integrated gastrin response to a meal reduced from 11 470 (1174) (pretreatment) to 8130 (608) pg/ml/h ($p < 0.05$). Fasting serum gastrin concentrations and maximal acid output reduced significantly only six months after eradication. In contrast, no significant change of any of these measurements was seen in the control group either at three or six months from healing compared with the pretreatment values. Gastric emptying of liquids did not change over the entire period of follow up in both study groups. In conclusion, eradication of *H pylori* in duodenal ulcer patients is accompanied by a rapid fall in serum pepsinogen I and plasma gastrin concentrations, whereas a slight but significant reduction of maximal acid secretion takes place later on. In contrast, gastric emptying of liquids does not seem to be influenced by *H pylori* status.

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Keywords: *Helicobacter pylori*, gastrin, pepsinogen, acid secretion, gastric emptying, duodenal ulcer.

Despite the fact that *Helicobacter pylori* is now recognised to be the most important acquired factor in the pathogenesis of duodenal ulcer disease,¹ the mechanisms by which the organism promotes ulcer remain unknown. The discovery that *H pylori* increases fasting and meal stimulated gastrin concentrations²⁻⁵ raised the possibility that the known abnormalities of acid secretion and gastric emptying that have been reported in duodenal ulcer

disease⁶ could be attributed to this infection. Unfortunately, to date the effect of *H pylori* on acid secretion remains controversial: a few authors, indeed, described a significant reduction of both basal⁷ and gastrin releasing peptide stimulated acid output after eradication of *H pylori*,⁸ whereas others found that *H pylori* eradication was not accompanied by any significant variation in basal, nocturnal, and pentagastrin stimulated acid secretion.⁹⁻¹¹ A number of reasons could be considered for this discrepancy: firstly, many studies did not distinguish between active and healed duodenal ulcer patients, whereas there is some evidence suggesting that acid secretion decreases after ulcer healing¹²⁻¹⁴; secondly, some studies were carried out on very small groups of patients, so that their results may be biased by the numerical inconsistency of the study population; thirdly, most studies tried to detect changes of acid secretion only after four weeks from *H pylori* eradication, although a reduction of the parietal cell mass or of its sensitivity, if any, could not be expected earlier than a few months from eradication; and finally, none of these studies included a control group of patients in whom *H pylori* had not been eradicated, who were prospectively followed up for a period of time long enough to exclude variations of acid secretion caused by factors unrelated to *H pylori* infection, such as vagal drive or cigarette smoking.^{15 16}

With regard to the effect of *H pylori* on gastric emptying in duodenal ulcer patients, to date no controlled study has evaluated the behaviour of such a parameter after *H pylori* eradication.

The aim of the study was, therefore, to evaluate the behaviour of acid secretion, serum pepsinogen I, gastrin release, and gastric emptying of liquids in a group of duodenal ulcer patients over six months from *H pylori* eradication, compared with that of a control group of duodenal ulcer patients with persistent *H pylori* infection.

Methods

Patients

Twenty eight consecutive outpatients (16 men and 12 women) with *H pylori* positive duodenal ulcer disease were initially recruited into the study. As entry criteria, they all had an active uncomplicated duodenal ulcer diagnosed at endoscopy, and *H pylori* infection determined

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by a biopsy urease test and histological assessment. None had a previous history of gastric surgery, concomitant gastric ulcer, or any serious medical illness, or had taken antibiotics or bismuth compounds during the previous six months. None of the patients had taken any medical treatment during the 15 days before initial endoscopy except for antacids. Each patient had a series of functional examinations including acid secretory tests, determination of basal and meal stimulated gastrin concentrations, as well as serum pepsinogen I concentrations, and measurement of gastric emptying of liquids (see later) before starting antiulcer treatment. Within six days from initial endoscopy, patients were assigned to receive an eradicating regimen consisting of lansoprazole 30 mg a day for one month, amoxicillin 1 g three times daily, and tinidazole 500 mg twice daily concurrently for the first two weeks of treatment, or lansoprazole 30 mg/day alone for four weeks according to a 3:2 randomisation list. Patients' compliance was evaluated by counting all the unused tablets brought back by patients at fortnightly clinical controls. Endoscopy with antral and corpus biopsies was repeated four weeks after the end of treatment. Gastric histopathology was evaluated without knowledge of treatment outcome and was classified according to the Sydney system.¹⁷ In particular, a detailed protocol was used to evaluate gastritis activity and total immune inflammatory cells in the antrum and corpus using four different categories of severity for each parameter (absent, mild, moderate, and severe). Patients were considered to have eradicated *H pylori* if both histology and urease rapid test in gastric antrum and corpus were negative.

All patients with healed ulcer regardless of *H pylori* eradication were offered the possibility of entering the study protocol, which comprised repetition of endoscopy with biopsies and all functional tests after three and six months from the second endoscopy as part of a one year longitudinal follow up study. No antiulcer drug was prescribed for patients with healed ulcer and persistent *H pylori* infection during the follow up period except for antacids when needed.

Measurement of acid secretion

On each study day, patients were admitted to the gastrointestinal clinic laboratory at 0900 after an overnight fast. A nasogastric tube (Salem, 18 Fr) was passed into the gastric antrum and its position checked by the water recovery test. After emptying the stomach, gastric juice was aspirated and collected using an intermittent suction unit that applies suction for 20 seconds in each 30 second cycle. Four 30 minute collections were obtained basally, then a subcutaneous injection of pentagastrin (Peptavlon, ICI, UK) 6.0 µg/kg was given, and gastric juice was collected in 15 minute batches for the following hour. Saliva was aspirated by a continuous suction pump and discharged. The H⁺ concentration was determined by titration to pH 7 with

NaOH 0.1 N using an autotitrator (Radiometer, Copenhagen). Basal acid output per hour was calculated by taking the mean of all four 30 minute samples before pentagastrin infusion. Maximal acid output (mmol/h) was calculated as the sum of the four consecutive 15 minute outputs, after pentagastrin infusion. Peak acid output was calculated as the sum of two consecutive highest 15 minute acid outputs multiplied by two. The secretory studies were all performed with the investigator blind to the *H pylori* state of the patients.

Measurement of gastrin and pepsinogen I

Serum gastrin was determined on a separate day from the acid secretory test, at fasting and after the ingestion of a standard protein meal consisting of 15 g of peptone dissolved in 150 ml water at 50°C, with venous blood samples taken at 15 minute intervals for 90 minutes. After the samples were allowed to clot, serum was removed and stored at -20°C. Gastrin concentrations were determined by a commercial radioimmunoassay kit (Incstar, Stillwater, USA) with a coefficient of variation of the assay of 3.8%. The basal gastrin value for each patient was determined by taking the mean of three samples taken at 15 minute intervals before the peptone meal. Meal stimulated gastrin release was expressed as the peak of concentration and as the integrated gastrin response to the meal; the second value was taken as the area under the serum gastrin time curve, calculated by the trapezoid method.

Serum pepsinogen I was determined at fasting, before starting treatment, and after three and six months from its finish by a commercial immunoassay (Sorin, Biomedica, Saluggia, Italy) with an intra-assay coefficient of variation of 5.5%. All samples were measured in duplicate in the same assay.

Determination of gastric emptying

Gastric emptying was measured on a day subsequent to those of the secretory and gastrin studies by two different methods: acetaminophen absorption and serial ultrasonographic measurements of the gastric antrum. On each day of examination, the patient ingested a standard liquid meal consisting of 13.2 g carbohydrates, 8.2 g protein, 1 g lipids, and 1.5 g acetaminophen in 200 ml of tap water (equivalent to 90 kcal and 398 mOsm) over two minutes. Ultrasonographic evaluation of the gastric antrum area and serial blood samples for acetaminophen absorption were taken simultaneously at 20 minute intervals from 0 to 80 minutes. Plasma acetaminophen was determined by homogeneous enzyme immunoassay technique¹⁸; the peak plasma concentration, the time to peak, and the area under the plasma concentration time curve of acetaminophen were used as an index of the emptying rate.¹⁹ As absorption of acetaminophen from the stomach is negligible, its absorption from the small intestine and therefore its appearance in the peripheral

TABLE I Pretreatment individual characteristics of the case and control group

	Case group	Control group	p Value
Sex (M/F)	5/6	5/3	
Age (y)	37.3 (3.5)	43.4 (6.1)	NS
Weight (kg)	68.7 (7.1)	66.7 (4.9)	NS
Duration of ulcer disease (month)	84 (19)	116 (25.5)	NS
Smoking			NS
>15 cigarettes/day	2	2	
0-15 cigarettes/day	2	3	
Non-smokers	7	3	
BAO (mEq/h)	7.8 (1.5)	6.8 (1.4)	NS
MAO (mEq/h)	33.9 (2.7)	34.4 (4.7)	NS
Serum gastrin			
Basal (pg/ml)	58.6 (4.1)	61.4 (7.1)	NS
Peak (pg/ml)	150.7 (17.9)	195.9 (55.1)	NS
AUC (pg/ml/h)	11470 (1174)	14558 (3730)	NS
Serum pepsinogen I (ng/l)	91.9 (6.9)	98.1 (7.0)	NS
Gastric emptying acetaminophen absorption (mcg/ml/h)	926.9 (94.6)	1100.1 (127.6)	NS

BAO=basal acid output; MAO=maximal acid output, AUC=area under curve. Data expressed as mean (SEM).

blood stream provides an indirect but accurate measurement of gastric emptying of liquid.

Ultrasonographic measurements of the gastric antrum were done by the same operator (GM or FP) using an Aloka 680 real time ultrasound instrument with a 3.5 MHz probe; gastric emptying was expressed as the sagittal antral area emptying ratio according to Bolondi *et al.*²⁰

Statistical evaluation

Results of functional tests are presented as mean (SEM) and statistical analyses were performed using the Student's *t* test for paired data. Student's *t* test for unpaired samples was used to compare the individual and baseline characteristics of the two groups of patients. Gastritis scores are reported as mean and range; statistical comparison between gastritis scores before and after treatment was made by the Wilcoxon rank sum test. A *p* value of <0.05 was taken to represent a statistically significant difference.

The study was approved by the local ethics committee and informed consent was obtained from each patient.

Figure 1: Mean scores, as based on four scale steps (0 to 3) of antral gastritis over the six month follow up in the case and control group. HP=H pylori colonisation; Inf=total inflammatory cell infiltrate; Act=neutrophilic granulocyte infiltrate; Atr=mucosal atrophy. Inf 0 v 3 months: *p*<0.05; Act 0 v 3 months: *p*<0.05.

Results

Clinical

Eighteen of 28 patients who initially entered the study received lansoprazole plus antibiotics and 10 lansoprazole alone. All but one patient completed the treatment correctly, with a compliance rate of never less than 80%; one patient receiving triple therapy defaulted because of side effects (diffuse skin rash) and was excluded from further evaluations. At repeated endoscopy ulcers had healed in all the cases, but triple therapy for *H pylori* resulted in successful eradication in 14 of 17 (82%) treated patients, whereas no patient in the monotherapy lansoprazole group eliminated *H pylori*. Eleven patients who were cured of *H pylori* infection and eight patients with persistent *H pylori* infection (all of the second group of patients treated with lansoprazole alone) accepted the invitation to enter the follow up protocol and therefore constituted the case and control groups respectively. Table I summarises the individual characteristics of these two groups. Data from these 19 patients were then analysed further on for the behaviour of gastric function indices over the following six months.

There were no duodenal ulcer relapses in any of the patients cured of *H pylori* infection during the follow up period, whereas one patient with persistent *H pylori* infection had asymptomatic duodenal ulcer recurrence at six months from healing.

Histological assessment

In the group of patients who eliminated *H pylori*, the mean activity score of gastritis in the antrum was 1.7 before treatment, and fell to 0.1 after three months from eradication (*p*<0.01); in the group of patients with persistent *H pylori* infection, the mean gastritis score was 1.5 before treatment and 1.1 and 1.3 after three and six months from healing respectively (*p*=NS, see Fig 1).

Basal and meal stimulated gastrin

Basal and meal stimulated pretreatment gastrin concentrations were similar in both study groups (Table I). In the 11 *H pylori* cured patients, the means of both peak and integrated gastrin response to meal but not fasting gastrin concentrations fell significantly three months after eradication, compared with the pretreatment values; after six months there was a numerical but not significant further fall in meal stimulated gastrin values in comparison with the three month values, whereas fasting gastrin concentrations reduced significantly compared with both the pretreatment and three month values. In contrast, no significant variation of basal and meal stimulated gastrin concentrations was seen in the eight patients with persistent *H pylori* infection over the entire follow up period (Table II).

Basal and maximal acid secretion rates

In the 11 patients where *H pylori* was

TABLE II Behaviour of gastric function indices during the six month follow up in the two groups

	Case group			Control group		
	Pretreatment	3 Months	6 Months	Pretreatment	3 Months	6 Months
BAO (mEq/h)	7.8 (1.5)	6.3 (0.8)	6.2 (0.5)	6.8 (1.4)	6.3 (1.8)	6.1 (1.2)
MAO (mEq/h)	33.9 (2.7)	33.0 (3.1)	28.4 (1.8)*	34.4 (4.7)	33.5 (3.6)	33 (3.5)
PAO (mEq/h)	42.6 (2.6)	42.0 (4.3)	35.3 (2.8)†	41.5 (6)	40.4 (4.7)	41.8 (4.3)
Serum gastrin						
Basal (pg/ml)	58.6 (4.1)	56.4 (3.8)	50.1 (2.9)‡	61.4 (7.1)	62 (7.1)	60 (4.8)
Peak (pg/ml)	150.7 (17.9)	96.7 (8.1)	79 (4.5)§	195.9 (55.1)	190.2 (49.6)	184.1 (43.5)
AUC (pg/ml/h)	11 470 (1174)	8130 (608)	7647 (564)	14 558 (3730)	12 834 (2294)	13 339 (2024)
Serum pepsinogen I (ng/l)	91.9 (6.9)	72.2 (5.1)	71.5 (4.1)¶	98.1 (7.0)	108.2 (13.4)	121.5 (14.1)
Gastric emptying acetaminophen absorption (mcg/ml/h)	926.9 (94.6)	1004.5 (80)	1136 (107.5)	1100.1 (127.6)	950 (78.8)	986.7 (84.5)

PAO=peak acid output. Other abbreviations as Table I. *0 v 6; $p<0.02$; 3 v 6: $p<0.05$. †0 v 6: $p<0.05$. ‡0 v 6: $p<0.05$; 3 v 6: $p<0.03$. §0 v 3: $p<0.02$; 0 v 6: $p<0.003$; 3 v 6: $p<0.05$. ||0 v 3: $p<0.02$; 0 v 6: $p<0.018$. ¶0 v 3: $p<0.001$; 0 v 6: $p<0.001$. Data expressed as mean (SEM).

eradicated, no significant changes were registered in their basal and stimulated acid secretion rates after three months, whereas at six months after *H. pylori* eradication, there was a significant reduction of maximal acid output in comparison with both pretreatment and three month values (Fig 2). In particular, the maximal acid output (mean (SEM)) fell from 33.9 (2.7) (pretreatment) to 28.3 (1.8) (six months) mEq/h ($p<0.02$), which is a reduction of about 16%. Similarly, peak acid output values fell from 42.6 (2.6) to 35.3 (2.8) ($p<0.05$).

There was also a tendency towards a numerical but not significant decrease of basal acid output at six months from eradication. In contrast, in the eight patients with persistent *H. pylori* infection, means of basal and maximal acid output both at three and six months from duodenal ulcer healing did not differ significantly from their correspondent pretreatment values.

Gastric emptying of liquids

The peak plasma concentration as well as the time to peak and the area under plasma concentration time curve of acetaminophen remained virtually unchanged over the entire period of follow up both in patients where *H. pylori* infection had been eradicated and those where it had not (Table II). Similarly, three and six months from ulcer healing the mean of

ultrasonographic antral area emptying ratio at 80 minutes did not differ significantly from the correspondent pretreatment value both in patients who eliminated *H. pylori* and in those with persistent infection (Fig 3).

Discussion

If, on the one hand, there is now a great deal of evidence showing that both duodenal ulcer patients and healthy volunteers with *H. pylori* have increased basal and stimulated gastrin concentrations that fall after eradication of the infection,²⁻⁵ on the other hand, the effects of *H. pylori* on acid secretion, especially in duodenal ulcer patients, remain to be clarified. A number of studies have already examined the effects of *H. pylori* eradication on basal and stimulated acid secretion, yielding conflicting results: indeed, in two studies with duodenal ulcer patients^{2 21} and in one study with dyspeptic patients,⁹ no significant changes of basal acid output were found after stopping anti-*H. pylori* treatment, whereas more recently, Moss and Calam⁷ and El-Omar *et al*⁸ reported a significant fall of basal acid output in duodenal ulcer patients one month after *H. pylori* eradication.

As far as the relation between *H. pylori* and stimulated acid secretion is concerned, some authors reported that maximal or peak acid output is not significantly changed by the eradication of *H. pylori*,^{7 9 21 22} whereas recently El-Omar *et al*⁸ found that in duodenal ulcer patients one month after *H. pylori* eradication, median acid output in response to gastrin releasing peptide decreased by a median of 66% in comparison with the pretreatment values. The results of many of these studies, however, should be interpreted with caution for several reasons: (a) the numerical inconsistency of the study population, which, in some papers, was restricted to only six patients²¹; (b) the lack of distinction between clearance and true *H. pylori* eradication, as in a few studies patients were re-tested within only one to two weeks of ending treatment, so that, in some cases, the infection may have persisted^{9 22}; (c) the status of duodenal ulcer disease on entering the study, as some studies included only patients with inactive ulcer, whereas others only enrolled patients with active disease; as there is some evidence that basal secretion may decrease after healing of ulcer by drugs that do not act on *H. pylori*,¹²⁻¹⁴ the fall in basal acid

Figure 2: Behaviour of basal (BAO) and maximal (MAO) acid secretion over the six month follow up in the case and control group.

Figure 3: Gastric emptying of liquids as evaluated by ultrasound over the six month follow up in the (A) case and (B) control group.

secretion seen by some authors after anti-infective treatment may not necessarily result from the eradication of *H. pylori*, but simply to the healing process itself^{7,8}; (d) the lack of a control group of duodenal ulcer patients with persistent *H. pylori* infection followed up for long enough to exclude causes of variations in acid secretion different to *H. pylori* eradication – that is, longterm effects of healing, modifications of vagal tone or cigarette smoking.^{14–16,23}

The results of our controlled study confirm once more that the eradication of *H. pylori* in duodenal ulcer patients is associated with a considerable reduction of both basal and meal stimulated plasma gastrin concentrations. Compared with previous reports, however, our paper adds further information on two important points. Firstly, the fall in meal stimulated gastrin concentrations reached its peak after three months from eradication but tended to continue after six months as well; in contrast, fasting concentrations of gastrin significantly reduced only after six months from eradication. This concurs partially with that seen by McColl *et al.*¹⁰ who monitored the gastrin release after *H. pylori* eradication for up to seven months; this group also noted an early significant fall of meal stimulated gastrin followed by a later sustained reduction of about 30% at seven months, which, however, did not reach statistical significance. The prolonged reduction of gastrin seen in our patients is consistent with the idea that gastric inflammation itself is responsible for *H. pylori* associated hypergastrinaemia²⁴ because the regression of the inflammatory infiltrate in gastric mucosa takes place slowly after eradication, as we have already reported.²⁵ An alternative explanation for the late fall of basal gastrin could be an associated hypergastrinaemia induced by lansoprazole treatment, which may last from one to 12 weeks after drug suspension²⁶; however, the fact that it did not occur in the control group weakens this hypothesis. Secondly, the significant fall in meal stimulated plasma gastrin seen after *H. pylori*

eradication is entirely due to the elimination of infection and is not a result of the ulcer healing process nor is it a consequence of the antiulcer treatment, as shown by the fact that it did not occur in the control group.

Despite the fast lowering of meal stimulated gastrin concentrations, maximal acid secretion decreased significantly in our series only after six months from *H. pylori* eradication. This late reduction of the parietal cell mass, however, concurs well with the slow fall in fasting gastrin concentrations, which exert a trophic effect on the oxyntic mucosa. Indeed, if we consider that the half life of a parietal cell is 23 days in mice²⁷ and perhaps longer in humans, a removal of the trophic effect of gastrin on parietal cells might not be apparent earlier than several months from eradication.

This study therefore supports the hypothesis that the eradication of *H. pylori* reduces in the longterm the gastric parietal cell mass, thus linking this bacterium with one of the important known abnormalities of acid secretion in duodenal ulcer disease. The fact that the fall in maximal acid secretion was only 16%, however, casts doubt on the unique role for *H. pylori* induced hypergastrinaemia in determining the increased parietal cell mass typical of duodenal ulcer disease. One clue to the reason for this apparent discrepancy could be that the eradication of *H. pylori* resolves only the component of increased acid secretion caused by the augmented gastrin, but not that sustained by other components. The increased parietal cell mass of duodenal ulcer patients may be caused by a combination of factors, which include: familial factors,⁶ vagal tone,¹⁵ cigarette smoking,^{16,23} in addition to the previously mentioned longterm trophic effect of *H. pylori* induced hypergastrinaemia on the oxyntic mucosa.

Another explanation could be that the reduction of *H. pylori* induced parietal cell hyperplasia takes much more than six months to be completed. Therefore, further studies with a longer monitoring time of acid secretion after *H. pylori* eradication are required to test this last hypothesis.

Our findings also confirm that eradication of *H. pylori* in duodenal ulcer patients is accompanied by a significant decrease in pepsinogen I values, as recently shown by other authors.^{28,29} This strengthens the view that hyperpepsinogaemia I, which has for a long time been regarded as a genetic marker for duodenal ulcer disease,³⁰ is more probably caused by a leakage into the blood of pepsinogen from chief cells inflamed by *H. pylori*.

An accelerated gastric emptying of liquids is another abnormality of the gastric function, which has been reported in duodenal ulcer patients by some authors^{31,32}; as there is some evidence that intramuscular administration of low dose gastrin might accelerate gastric emptying in healthy volunteers,³³ it has been hypothesised recently that *H. pylori* induced hypergastrinaemia is responsible for the accelerated gastric emptying found in duodenal ulcer.³⁴ In contrast, our results show that eradication of *H. pylori* is not associated with

significant modifications of gastric emptying of liquids, at least within six months of follow up. It should be emphasised, however, that we studied gastric emptying of a liquid hypocaloric/hypoproteic test meal, whereas a modification of emptying, through a gastrin pathway, if any, could be better evaluated using a protein rich test meal, which would exert a potent stimulus on gastrin release and acid secretion. Therefore, further studies are necessary to investigate the longterm potential effect of *H. pylori* eradication on both the liquid and the solid phase of gastric emptying in duodenal ulcer patients.

In conclusion, our study confirms that in duodenal ulcer patients serum pepsinogen I and plasma gastrin concentrations fall rapidly after eradication of *H. pylori*, whereas a slight but significant reduction of stimulated acid secretion takes place later on. This is not accompanied by any significant modification of gastric emptying of liquids.

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