

Eradication of *Helicobacter pylori* in patients with duodenal ulcer lowers basal and peak acid outputs to gastrin releasing peptide and pentagastrin

A W Harris, P A Gummert, J J Misiewicz, J H Baron

Abstract

Background—Patients with duodenal ulcer (DU) have high basal (BAO) and peak (PAO) acid outputs. The effect of *Helicobacter pylori* eradication on these variables is unclear.

Aim—To discover if gastric acid hypersecretion in patients with DU is caused by *H pylori*.

Patients and methods—BAO, gastrin releasing peptide (GRP), and pentagastrin stimulated PAO in 10 *H pylori* negative controls, and in 10 *H pylori* positive patients with DU was measured before and six months after *H pylori* eradication. *H pylori* status was determined by histology, culture, and by the ¹³C-urea breath test. After collecting a 30 minute basal aspirate, GRP 40 pmol/kg/h was infused for 45 minutes, and after a 30 minute washout, pentagastrin 6 µg/kg was injected intramuscularly.

Results—Basal and stimulated acid output (PAO_{GRP} and PAO_{Pg}) were significantly higher in *H pylori* positive DU than in *H pylori* negative controls. Six months after *H pylori* eradication, basal and stimulated acid outputs were all significantly lower than before *H pylori* eradication.

Conclusions—This study has shown that BAO, PAO_{GRP}, and PAO_{Pg} are higher in *H pylori* positive DU than in *H pylori* negative controls. All decreased significantly six months after *H pylori* eradication, to fall within the range of controls. These results are compatible with a hypothesis that acid hypersecretion in duodenal ulcer disease is caused by *H pylori* infection.

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Keywords: *Helicobacter pylori*, gastric acid output, gastric releasing peptide.

Helicobacter pylori is found in more than 95% of patients with duodenal ulcer (DU) and its eradication decreases recurrence of DU from 80% to less than 2% in 12 months.¹ Both *H pylori* and acid hypersecretion have a role in the pathogenesis of DU, but it is not clear whether gastric acid hypersecretion in DU is caused by this infection.

Patients with DU have about double normal basal (BAO) and stimulated peak acid outputs (PAO),² but the effect of *H pylori* eradication on these variables is unclear. Two groups of investigators have reported a significant fall in BAO.^{3,4} A 66% decrease in gastrin releasing peptide (GRP) stimulated PAO (PAO_{GRP}), in patients with DU one month after *H pylori* eradication was also recorded.⁴ However, other studies have not shown significant changes in BAO or pentagastrin stimulated PAO (PAO_{Pg}) in patients with DU studied up to one year after *H pylori* eradication (Table I).^{3,5-7} We have therefore measured BAO, PAO_{GRP}, and PAO_{Pg} in *H pylori* negative controls and *H pylori* positive patients with DU before and six months after *H pylori* eradication.

Subjects and methods

We studied *H pylori* negative healthy volunteers without dyspepsia and with a normal endoscopy, and 10 *H pylori* positive patients with symptomatic and endoscopically diagnosed DU. Eight of 10 patients with DU were restudied six months after *H pylori* eradication with omeprazole 20 mg twice daily and amoxicillin 1 g twice daily, given for two weeks (Table II). None of the subjects had taken antisecretory medication within seven days of the studies and the patients with DU had not taken non-steroidal anti-inflammatory drugs (NSAIDs). The proportions of cigarette smokers in the two groups were similar.

Determination of *H pylori* status

H pylori status was determined by histology (antral, body, and duodenal bulb biopsy specimens routinely processed and stained

Parkside Helicobacter Study Group, Central Middlesex and St Mary's Hospitals, London
A W Harris
P A Gummert
J J Misiewicz
J H Baron

Correspondence to:
Dr A Harris, Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London NW10 7NS.

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TABLE I Acid secretion (mmol/h) before and after *H pylori* eradication

Reference	Number	<i>H pylori</i> positive DU			After <i>H pylori</i> eradication			Follow up (months)
		BAO	PAO _{GRP}	PAO _{Pg}	BAO	PAO _{GRP}	PAO _{Pg}	
Present study	10	9	31	43	3*	11*	29*	6
El-Omar <i>et al</i> ⁴	11	6.6	37		3.6*	13.7*		1
El-Omar <i>et al</i> ⁴	8		38			7.5*		12
Fullarton <i>et al</i> ⁵	8	10.7		34.7	6.7		30	1
	(6)				(10)		(31)	(12)
Levi <i>et al</i> ¹³	10	4.1		46.4	4.5		46	<1
Moss <i>et al</i> ⁶	6	6.3		46	3.8		48	12
Moss <i>et al</i> ³	9	8.3		37	2.6*		37	1
Chiba <i>et al</i> ⁷	12	7.9		45.5	6.1		34.5	1
Graham ²⁹	1	7.8		52	3.8		34.5	12

*Denotes significant decrease ($p < 0.05$) after *H pylori* eradication. Acid outputs are expressed as means or medians depending on the original data. Figures in parentheses refer to a 12 month follow up study on six of eight patients studied at one month.

TABLE II Details of subjects studied

Group	Controls	DU	DU follow up
Endoscopy	Normal	DU	Normal
<i>H pylori</i> status	Negative	Positive	Negative
Patients (n)	10	10	8
Men	4	7	6
Age mean (range) (y)	33 (24-40)	37 (22-58)	39 (24-58)
Current smokers	2	3	3

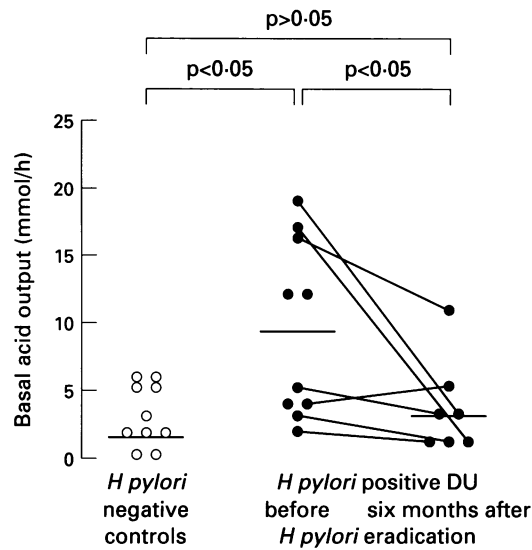


Figure 1: Basal acid output in *H pylori* negative controls (○) and patients with DU (●) before and six months after *H pylori* eradication. Horizontal bars are medians.

with haematoxylin and eosin and Gimenez stains), culture (antral and duodenal bulb specimens isolated in selective and non-selective media, and microaerobic conditions for up to 10 days), and by the ^{13}C -urea breath test (European Standard Protocol, where a result is positive if excess $\delta^{13}\text{CO}_2$ excretion exceeds 5 per mil⁸). Subjects were defined as *H pylori* positive if the breath test and at least one other test was positive, and *H pylori* negative if the breath test, histology, and culture were negative.

Gastric acid output

Gastric secretion studies were performed using a standard method.² Within seven days of the endoscopy and after an overnight fast, a nasogastric tube (Salem sump tube, 90–120 cm long, 10–14 French, Sherwood Medical, West Sussex) was positioned in the most dependent part of the stomach by the water recovery test. The stomach was aspirated continuously using a suction pump (KV-4, Keymed Limited, Essex) at a negative pressure of 30 to 50 mm Hg. GRP (Cambridge Research Biochemicals, Cheshire, England) was purchased in 0.5 mg aliquots of freeze dried lyophilised powder and prepared by the Central Middlesex Hospital Pharmacy under sterile conditions. Each aliquot was made up according to the supplier's instructions, into a one litre stock solution by dissolving in 0.9% sodium chloride; 25 ml of 5% albumin was added to stabilise the solution.

The stomach was emptied and one 30 minute basal aspirate was collected. Immediately after the BAO collection, GRP was infused into a dorsal vein of the hand using a syringe driver (Flo-Gard DSP, Baxter Healthcare, Berkshire) at 40 pmol/kg/h for 45 minutes; three consecutive 15 minute stomach aspirates were collected.⁹ The GRP infusion was followed by a 30 minute unstimulated period to allow plasma GRP concentrations to return to normal,^{10–12} while gastric secretion

was continuously aspirated and discarded. Immediately after the unstimulated period, pentagastrin 6 $\mu\text{g}/\text{kg}$ (Peptavlon, ICI Pharmaceuticals, Cheshire, England) was injected into the triceps muscle and three consecutive 15 minute aspirates collected. Four subjects (two in each group) experienced transient nausea after the pentagastrin injection, but recovered fully. No adverse effects were reported during GRP infusion.

All aspirates were stored at +4°C until analysed. Titratable acidity (mmol/l) was measured with a Metrohm auto-titrator (V A Howe and Co, Banbury, England) by titration to pH 7.0 with 0.01 M sodium hydroxide. Acid output (mmol/h) was calculated as the product of volume (l) and titratable acidity (mmol/l). The two consecutive 15 minute samples with highest acid secretion were used to calculate 30 minute peak acid output, which was then doubled and expressed as mmol/h.²

Statistical methods

Normally distributed data are expressed as means and Student's unpaired *t* test used to compare the significance of the difference between the group means. Acid outputs are non-Gaussian and data were expressed as medians and ranges. Wilcoxon signed rank (for paired) and Mann-Whitney (for unpaired) tests were used to compare the significance of the difference between the group medians, where $p < 0.05$ was considered to be statistically significant.

Ethics

The protocol was approved by the Parkside ethical committee and all subjects gave written informed consent.

Results

Basal (BAO) and stimulated (PAO_{GRP} , PAO_{Pg}) acid outputs (mmol/h) were significantly ($p < 0.05$) higher in *H pylori* positive patients with DU than *H pylori* negative controls, with median (range) BAO 9 (2–19) *v* 2 (0.2–6), PAO_{GRP} 31 (0.3–55) *v* 11 (1–25) and PAO_{Pg} 43 (19–69) *v* 22 (12–40), respectively (Figs 1–3).

Of the 10 patients with DU, eight agreed to be restudied after *H pylori* eradication. At endoscopy all DUs had healed, with no evidence of duodenitis. BAO and PAO_{GRP} are available for seven of these eight patients, due to a technical error in one. Six months after *H pylori* eradication, median (range) BAO, PAO_{GRP} , and PAO_{Pg} were 3 (1–11), 11 (0.9–39), and 29 (8–52), respectively (Figs 1–3); all significantly ($p < 0.05$) lower than before *H pylori* eradication, and not significantly different from the outputs in the *H pylori* negative controls.

The median (range) per cent decrease after eradication of *H pylori* was not significantly different for the three variables of acid output measured: BAO 50% (20–94), PAO_{GRP} 55% (15–60), and PAO_{Pg} 33% (9–76).

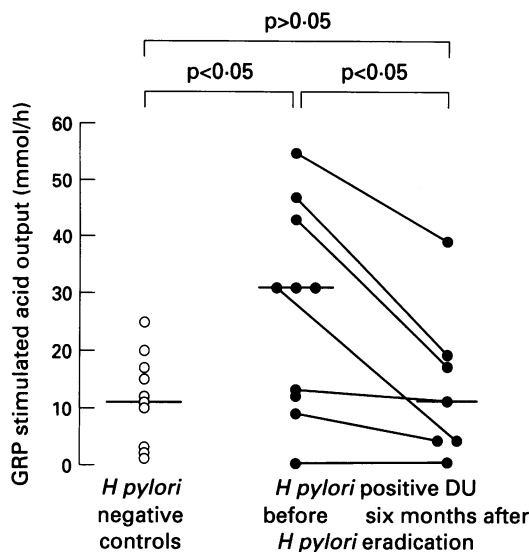


Figure 2: GRP stimulated peak acid output in *H pylori* negative controls (\circ) and patients with DU (\bullet) before and six months after *H pylori* eradication. Horizontal bars are medians.

Discussion

This study has shown that basal, GRP, and pentagastrin stimulated acid outputs are higher in *H pylori* positive patients with DU than in *H pylori* negative controls, but decrease significantly six months after *H pylori* eradication and DU healing, to fall within the range of controls.

BAO

As expected, *H pylori* positive patients with DU in this study had significantly higher median BAO than *H pylori* negative controls. Six months after *H pylori* eradication BAO fell by a median of 50%, to within the range of *H pylori* negative controls. These findings agree with those of Moss *et al*³ and El-Omar *et al*⁴ (Table I). Fullarton *et al*⁵ could not show a significant fall in BAO one month after *H pylori* eradication in eight (seven female) patients with DU. Mean BAO (10.7 mmol/h) in this group of predominantly female patients with DU is higher than that reported by others in *H pylori* positive patients with DU,^{3 4 6 7 13} and may represent a subset of patients with gastric acid basal hypersecretion.

PAO_{GRP}

El-Omar *et al*⁴ infused GRP 40 pmol/kg/h for 45 minutes in nine *H pylori* negative controls and 11 *H pylori* positive patients with DU and found the median acid output (mmol/h) in the *H pylori* positive patients with DU (37, range 8.5–57) was about six times that of the controls (5.5, range 1–9). One month after *H pylori* eradication acid output in these patients fell by a median of 66% to a median value of 13.7 mmol/h (range 6.2–24) ($p < 0.01$), and fell further to 7.5 mmol/h (median 80% fall) at the end of one year (Table I).¹⁴ Our results confirm those of El-Omar *et al*, in that the *H pylori* positive patients with DU have an exaggerated acid response to GRP. However, the median PAO_{GRP} acid output in *H pylori* positive

patients with DU (31, range 0.3–55) in this study was only about threefold higher than in the *H pylori* negative controls (11, range 1–25). These differences in the magnitude of GRP stimulated acid output between the two studies may be due to technical factors (McCull's group used acetic acid to stabilise the GRP solution, while albumin was used in this study), or to differences in the patient populations (Glasgow has a high incidence of severe DU), but do not change the general pathophysiological import of the findings.

It is interesting to compare the data in this study with those of Hirschowitz *et al*.¹⁵ They studied the acid response to bombesin in patients with DU and healthy volunteers before the discovery of *H pylori*. Acid output to bombesin was increased about threefold in the patients with DU in agreement with the results of this study, but again in contrast with the sixfold increase reported by El-Omar *et al*.⁴

One of the *H pylori* positive patients with DU had a very low acid output to GRP (0.3 mmol/h), possibly as a result of technical error, but excluding this value did not change the overall results. McCull's group have never found a GRP stimulated acid output in *H pylori* positive patients with DU of less than 15 mmol/h (personal communication), which would explain their minimal overlap with *H pylori* negative controls. In contrast, in this study, four of 10 *H pylori* positive patients with DU had PAO_{GRP} of less than 15 mmol/h, and five of the values were within the range of *H pylori* negative controls. In our study PAO_{GRP} fell by a median of 55% (similar to El-Omar *et al*⁴) to a median value of 11 mmol/h at six months after *H pylori* eradication. It may be that PAO_{GRP} initially falls rapidly during the first month after *H pylori* eradication and then decreases more slowly thereafter.

Kovacs *et al*¹⁶ measured PAO_{GRP} (50 pmol/kg/h) in eight *H pylori* positive patients with DU and 16 *H pylori* negative controls, and could not show any significant differences in acid secretion between the two groups.

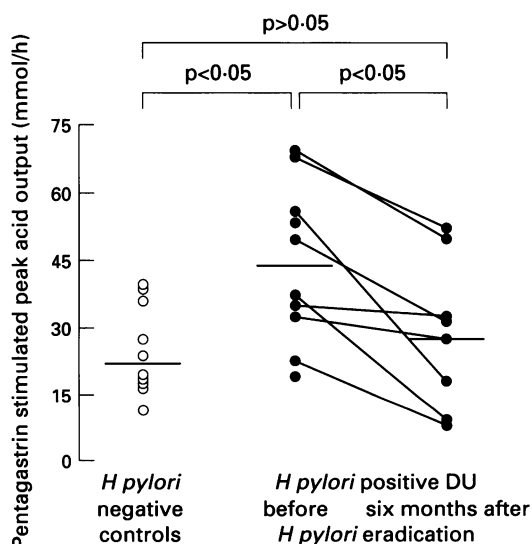


Figure 3: Pentagastrin stimulated peak acid output in *H pylori* negative controls (\circ) and patients with DU (\bullet) before and six months after *H pylori* eradication. Horizontal bars are medians.

Somewhat surprisingly, there was no significant difference in PAO_{Pg} between their patients with DU and their healthy controls. The reasons for these discordant results are unclear.

PAO_{Pg}

Peak acid output after a maximal dose of pentagastrin is a measure of the total population of functional parietal cells,¹⁷ unlike PAO_{GRP} , which measures the combined functional response of the antrum (G and D cells) and body (parietal cells) to endogenous gastrin.¹⁸ Chronic *H pylori* infection is associated with hypergastrinaemia, which returns to within the range of *H pylori* negative controls after *H pylori* eradication.⁴ Gastrin has a trophic effect on parietal cells and may increase their number in patients with DU,¹⁹ leading to an increase in PAO_{GRP} in *H pylori* positive patients with DU,^{3 5-7} as first proposed by Levi *et al.*²⁰

The hypothesis under test was that PAO_{Pg} would decrease after *H pylori* eradication: it did. However, Moss *et al.*³ and Chiba *et al.*⁷ could not show a significant fall in PAO_{Pg} one month after *H pylori* eradication (Table I). In this study PAO_{Pg} was re-measured six months after *H pylori* eradication. This suggests that the lack of change in earlier studies may have been due to a short follow up period. The half life of parietal cells in mice is between 23–42 days^{21 22} and probably longer in humans. Thus it could take many months for the trophic effect of the *H pylori* induced hypergastrinaemia on parietal cells to decrease; our data suggest that this has occurred by six months. Nevertheless, two groups^{5 6} have measured PAO_{Pg} one year after *H pylori* eradication, but did not record any significant changes (Table I). Moss *et al.*⁶ found no significant change in PAO_{Pg} one year after *H pylori* eradication in six patients with DU. They report 33% *H pylori* reinfection at one year, which is very high in comparison with other published data. It may be that their diagnostic methods (antral rapid urease test) used to determine *H pylori* status produced a high incidence of false negatives, making it possible that PAO_{Pg} was measured in both *H pylori* negative and positive patients. Fullarton *et al.*⁵ could not show significant changes in MAO_{Pg} one year after *H pylori* eradication in patients with DU (n=6). Surprisingly, only one of their eight patients with DU was male, so that at follow up at least five of six were women. This female predominance might explain the comparatively low MAO_{Pg} (34.7 mmol/h) at the start of the study. As DU is about four times commoner in men than women, it is possible that the preponderance of women in this study may represent an atypical subset of DU disease.

In this study PAO_{Pg} was measured 30 minutes after an infusion of GRP. A 30 minute interval after the end of the GRP infusion and before pentagastrin was based on pharmacokinetic studies of GRP/bombesin (closely related to GRP with similar effects on gastrointestinal function²³) intravenous infusions in humans.

These had shown that plasma gastrin and GRP concentrations return to pre-infusion values by 30 minutes after the end of GRP/bombesin infusions.^{10 11} Ghate *et al.*¹⁰ infused bombesin (0.75 and 2.4 pmol/kg/min) and found a rapid decline of plasma bombesin, with disappearance half time of about three minutes. Plasma gastrin concentrations increased during bombesin infusions, but returned to pre-infusion values within 30 minutes of stopping the bombesin. Wood *et al.*¹¹ infused GRP at about 40 pmol/kg/h in six healthy human volunteers. GRP produced a large rise in plasma GRP and gastrin, which both returned to pre-infusion values within 30 minutes of stopping the GRP infusion. Finally, a study using bombesin infusion showed that pentagastrin stimulated acid output returned to pre-bombesin values within 20 minutes of stopping the bombesin.¹²

On the basis of this information it was felt that a 30 minute washout was enough to ensure that the GRP test did not interfere with the pentagastrin test. Furthermore, since the initial publication of our results,²⁴ two other groups have confirmed our findings that pentagastrin stimulated peak acid output falls significantly after eradication of *H pylori*.^{25 26} Neither of these investigators used the GRP test before pentagastrin.

What is the significance of the fall in BAO, PAO_{GRP} , and PAO_{Pg} ? It has been recognised for some time that patients with DU have higher acid outputs² and a larger parietal cell mass¹⁷ than controls. The importance of acid hypersecretion in the pathogenesis of DU is underlined by healing of DU on treatment with antisecretory drugs; longterm inhibition of acid can prevent recurrence of DU. Eradication of *H pylori* heals and decreases recurrence of DU.¹ Our findings suggest that this may be related, at least in part, to decreased acid output. *H pylori* infection probably impairs the inhibitory control of gastric acid secretion, thought to be mediated largely through somatostatin.²⁷ The increased PAO_{GRP} in *H pylori* positive patients with DU may be caused by a combination of exaggerated gastrin release and acid response to gastrin as a result of impaired inhibition from somatostatin.¹⁴ Our findings and those of El-Omar *et al.*¹⁴ have shown that this abnormal response to GRP resolves after *H pylori* eradication, probably from increased somatostatin release after *H pylori* eradication.²⁷ The fall in PAO_{Pg} after *H pylori* eradication may be caused by decreased parietal cell mass, but other factors, such as decreased sensitivity of the parietal cells to gastrin, cannot be ruled out.

In summary, our findings have confirmed that basal and stimulated acid outputs are increased in *H pylori* positive patients with DU, and that BAO and PAO_{GRP} decrease significantly six months after *H pylori* eradication and DU healing, to fall within the range of controls. Furthermore, we have shown a significant decrease in PAO_{Pg} in *H pylori* positive patients with DU after *H pylori* eradication. These findings are compatible with a

model that acid hypersecretion in duodenal ulcer disease is caused by *H pylori* infection. Ulcer healing and decreased incidence of relapse of DU after *H pylori* eradication must thus depend, at least in part, on smaller amounts of acid reaching the duodenal bulb; but other factors, such as resolution of inflammatory changes in the gastric mucosa,²⁸ could also be important.

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