Effect of *Helicobacter pylori* infection on 24 hour intragastric acidity in patients with gastritis and duodenal ulcer

S Wagner, U Gladziwa, K Haruma, M Varrentrapp, M Gebel

Abstract

Helicobacter pylori status, gastric histology, and 24 hour acidity were studied in 35 gastritis patients, 21 duodenal ulcer patients, and 14 subjects with normal gastric mucosa. *H. pylori* was identified in 21 of 35 patients with chronic active gastritis and in 19 of 21 duodenal ulcer patients, but in none of those with normal gastric mucosa. Mean scores of activity of gastritis were similar in *H. pylori* positive gastritis and duodenal ulcer patients, but were significantly lower in *H. pylori* negative gastritis patients (2.1 (0.8) and 2.3 (0.9) v 1.4 (0.7); $p < 0.01$, respectively). Median 24 hour hydrogen ion activity (interquartile range) was 21 (8.9-38.0) mmol/l in normal subjects and 23 (11.2-49.0) mmol/l, 19 (7.1-33.1) mmol/l, 44 (25.1-63.1) mmol/l, and 36 (31.6-39.8) mmol/l respectively in gastritis and duodenal ulcer patients with and without *H. pylori* infection. During all predefined time periods, intragastric acidity was significantly higher in patients with *H. pylori* positive duodenal ulcers compared with gastritis patients and normal subjects. However, there was no significant difference in intragastric acidity between the *H. pylori* positive and negative gastritis patients. These results suggest that most of the subjects with chronic *H. pylori* infection have normal gastric acidity.

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gastric acidity in patients with gastritis and active duodenal ulcer disease.

Methods

STUDY SUBJECTS

Informed consent was obtained from each subject taking part in this study, in accordance with the declaration of Helsinki (1964) as revised in Tokyo (1975). Adult patients undergoing upper gastrointestinal endoscopy for routinely accepted clinical indications were considered for entry into the study if endoscopy showed a duodenal ulcer, gastritis, or normal mucosa. Routine biopsies were performed when indicated. For the study, separate biopsy specimens were obtained from the lesser curve of the antrum for the detection of *H. pylori* and for histopathological classification.^{20,21} The subjects were finally categorised into three groups according to their endoscopic and histopathological findings as follows: (i) active duodenal ulcer (endoscopic diagnosis); (ii) gastritis (histologically classified²¹); and (iii) normal (if both endoscopy and histology were normal). The subjects did not have complications of peptic ulcer disease; previous gastric surgery; concomitant treatment with ulcerogenic drugs, anticoagulants, or antibiotics; or any serious chronic disease. Only patients who had had no antibiotic treatment in the previous six months were included. Gastritis patients who had a medical history of ulcers were excluded.

ENDOSCOPY

At each endoscopy (Olympus GIF Q 20, Olympus Corp) at least five biopsy specimens were taken with sterilised biopsy forceps from the antral mucosa. Two specimens were placed in 2 ml phosphate buffered saline at 4°C for bacteriological examination, two were fixed in 10% formalin for histopathology, and one specimen was used for a rapid urease detecting test (CLO-test, Delta West Ltd, Australia). In addition, smears of biopsy specimens were made for cytological examination using Giemsa staining.

H PYLORI SCREENING

H. pylori status was assessed by bacterial culture, a modified Giemsa stain, and the CLO-test as described previously.^{20,21} Two biopsy specimens were cultured for seven days under microaerobic conditions in blood agar base containing 5% horse blood and Skirrow selective supplement. Cultures were considered positive for *H. pylori*

Department of
Gastroenterology and
Hepatology,
Medizinische
Hochschule Hannover,
D-3000 Hannover, 61
Germany
S Wagner
M Varrentrapp
M Gebel

Department of Medicine,
Rheinisch-Westfälische
Technische Hochschule
Aachen, D-5100 Aachen,
Germany
U Gladziwa

The First Department of
Internal Medicine,
Hiroshima University
School of Medicine,
Hiroshima 734, Japan
K Haruma

Correspondence to:
Dr Siegfried Wagner, Dept of
Gastroenterology and
Hepatology, Medizinische
Hochschule Hannover,
Konstanty Gutschowstr 8,
D-3000 Hannover 61, Federal
Republic of Germany.

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A causative role is now generally accepted for *Helicobacter pylori* in type B gastritis, and evidence is accumulating that *H. pylori* infection plays a major contributory part in peptic ulcer disease.^{1,2} It has been shown that eradication of *H. pylori* is associated with a significant reduction in the duodenal ulcer relapse rate.³⁻⁵ Since, on average, duodenal ulcer patients secrete more acid than control subjects, Levi *et al* have suggested that *H. pylori* causes duodenal ulcer disease by stimulating antral mucosal gastrin release which increases gastric acid secretion.⁶ While inappropriate hypergastrinaemia has been shown in subjects infected with *H. pylori*, the effect of *H. pylori* infection on gastric acidity remains controversial.^{7-14,19} Acute infections may lead to a transient hypochlorhydria.¹⁵⁻¹⁸ By contrast, in chronic infections large variations in gastric acidity have been reported, including hypochlorhydria, hyperchlorhydria, and normal acid secretion.^{6-14,19} There is, however, a paucity of data relating gastric acidity to the presence of chronic *H. pylori* infection. Because of this we have studied the effect of gastric *H. pylori* infection on the circadian pattern of

if Gram negative, oxidase positive, catalase positive, and urease positive spiral rods were present. The degree of colonisation with *H. pylori* was estimated by examination of sections and smears stained with Giemsa and was graded semiquantitatively. *H. pylori* status was regarded as positive if the culture was positive and/or if the urease test and Giemsa stain were positive.²¹

HISTOPATHOLOGY

For histological examinations formalin fixed biopsy samples were embedded in paraffin and 4 µm sections were stained with haematoxylin-eosin and Giemsa. Each biopsy specimen was assessed for the presence, type, density, and localisation of the inflammatory infiltrate. The degree of activity of gastritis was graded by estimating the density of polymorphonuclear leukocyte infiltrates as described previously.²¹ Gastritis scores of *H. pylori* positive patients and of uninfected patients were compared using Student's *t* test.

GASTRIC PH MONITORING

Gastric acidity was measured within three days of endoscopy. Intragastric pH was measured with a combined glass electrode (Ingold type 440 M4, Ingold AG, Urdorf, Switzerland) connected to a portable solid state recorder (Digitrapper 6200 MII, Syntectics Medical, Stockholm, Sweden) as described recently.²² The pH measuring unit was calibrated at 37°C using standard buffer solutions of pH 6.70 and 1.11 (Syntectics Medical). After each run, calibration was repeated for assessment of the drift of the electrode.

All study subjects were admitted to our gastrointestinal unit at 5 pm, having fasted since 3 pm. The electrode was fluoroscopically placed in the gastric corpus (8–10 cm below the cardia). Measurement began at 6 pm and lasted for 24 hours. All subjects were ambulatory. The conditions were standardised with regard to meal timing and composition (dinner at 6 pm, breakfast at 8 am; lunch at noon).²² Water and unsweetened tea were allowed during meals. No antisecretory treatment and no antacids were allowed during the pH study. In the case of severe pain, duodenal ulcer patients were allowed to take antacids; but these pH recordings were excluded from the final analysis of gastric acidity. Normal daily activities were unrestricted. All

study subjects marked their activities, meals, and special events in a diary card.

DATA PROCESSING AND STATISTICS

The pH measurements were stored every 4 seconds and the collected data were transferred to an IBM computer (AT 286). The recorded data were analysed for predefined time periods (total 24 hour: 6 pm–6 pm; evening: 6 pm–10 pm; night: 10 pm–6 am; morning: 6 am–12 noon; afternoon: 12 noon–6 pm).²² Median pH and median hydrogen ion activity and interquartile ranges were calculated for individuals and groups. For graphical presentation the medians of pH values averaged over 10 minute periods were used. Differences between the different time periods of duodenal ulcer and gastritis patients and normal subjects were assessed by Wilcoxon's rank sum test. In addition, the integrated area under the curve (AUC) for each 24 hour pH profile was calculated using the trapezoidal rule. AUCs were compared using Wilcoxon's rank sum test. Probability values $p < 0.05$ were considered significant.

GASTRIN ASSAY

A fasting blood sample was obtained from the subjects at entry to the study for measurement of serum gastrin by a commercial radioimmunoassay (Dinabot Company, Tokyo, Japan; normal range: 49.4–126.2 pg/ml). Serum gastrin concentrations of *H. pylori* positive patients and of uninfected patients were compared using Student's *t* test.

Results

H. pylori status, gastric histology, and 24 hour acidity were studied in 35 gastritis patients, 21 duodenal ulcer patients, and in 14 subjects with normal gastric mucosa. *H. pylori* was identified in 21 of 35 patients with chronic active gastritis, and in 19 of 21 duodenal ulcer patients, but in none of those with normal gastric mucosa (Table I). Sex ratio and smoking habits were comparable within the three groups. Mean age was somewhat lower in *H. pylori* negative subjects; this difference reached statistical significance in normal subjects only (Table I). Gastritis scores were similar in infected gastritis and duodenal ulcer patients, but were significantly lower in uninfected gastritis patients. Fasting serum gastrin was lower in *H. pylori* negative patients, but this difference was only statistically significant in the normal subjects.

Median 24 hour hydrogen ion activity (interquartile range) was 21 (8.9–38.0) mmol/l in normal subjects and 23 (11.2–49.0) mmol/l, 19 (7.1–33.1) mmol/l, 44 (25.1–63.1) mmol/l, and 36 (31.6–39.8) mmol/l respectively in gastritis and duodenal ulcer patients with and without *H. pylori* infection. The 24 hour median pH profiles of patients with gastritis and duodenal ulcer are shown in the Figure. *H. pylori* infection did not have a significant effect on the pattern of the pH profiles in either patient group. However, the gastric pH was constantly lower in *H. pylori* positive duodenal ulcer patients compared with

TABLE I *Helicobacter pylori* (HP) status and characteristics of patients with gastritis, duodenal ulcer, and normal gastric mucosa

	Gastritis		Duodenal ulcer		Normal
	HP+ve	HP-ve	HP+ve	HP-ve	HP-ve
No	21	14	19	2	14
Men/women	12/9	7/7	11/8	2/0	7/7
Age (mean (SD)) (yrs)	49 (11)	42 (10)	44 (11)	38 (8)	39 (11)*
Smokers (no)	9	7	9	2	5
Gastritis activity score (mean (SD))	2.1 (0.8)	1.4 (0.7)†	2.3 (0.9)	1.5 (0.7)	0
Gastrin (pg/ml, mean (SD))	108 (38)	88 (26)	115 (31)	99 (21)	74 (22)*

* $p < 0.05$ normal *v* gastritis HP+ve,

† $p < 0.05$ gastritis HP-ve *v* gastritis HP+ve

Median 24 hour pH profiles of patients with *Helicobacter pylori* (HP) positive duodenal ulcer (DU) and HP positive gastritis (A), HP positive and negative gastritis (B), and HP positive and negative duodenal ulcer (C).

H. pylori positive gastritis patients. This difference was most prominent during meals and during the nocturnal fasting period. The pH profile of the subject with normal gastric mucosa resembled that of the gastritis patients (not shown).

A quantitative analysis of the pH profiles showed that the intragastric pH was significantly lower in duodenal ulcer patients during all predefined time periods when compared with gastritis patients and normal subjects (Table II and III). The integrated AUCs of the 24 hour pH profiles of the infected duodenal ulcer patients were significantly lower than those of the *H. pylori* positive and negative gastritis patients and those of the normal subjects as well. However, the AUCs were similar in subjects with normal

gastric mucosa and both gastritis subgroups, showing that there is no difference in the acidity profiles of *H. pylori* positive and negative gastritis patients.

Discussion

This study shows that intragastric acidity is essentially the same in patients with chronic active gastritis, irrespective of their *H. pylori* status, and in subjects with normal gastric mucosa. In addition, our study confirms previous findings of an increased gastric acidity in duodenal ulcer patients.²²⁻²⁷ *H. pylori* negative duodenal ulcers were very rare, allowing pH monitoring in only two patients who showed acidity similar to the *H. pylori* positive duodenal ulcer patients.

In agreement with previous work,^{6,9,13} our *H. pylori* positive patients had higher fasting serum gastrin levels than the uninfected subjects. It is now well established that *H. pylori* infection is associated with inappropriate hypergastrinaemia

TABLE II Median pH and interquartile ranges for different time periods in gastritis and duodenal ulcer patients and subjects with normal gastric mucosa, and influence of *H. pylori* (HP) infection

	24 hour	Evening	Night	Morning	Afternoon
	6 pm-6 pm	6 pm-10 pm	10 pm-6 am	6 am-12 pm	12 pm-6 pm
Normal (n=14)	1.67 (1.42-2.05)	1.98 (1.60-2.94)	1.50 (1.30-2.08)	1.72 (1.55-1.98)	1.68 (1.42-2.00)
Gastritis (HP+) (n=21)	1.63 (1.31-1.95)	1.89 (1.56-3.20)	1.50 (1.35-1.98)	1.69 (1.51-1.99)	1.64 (1.50-2.05)
Gastritis (HP-) (n=14)	1.72 (1.48-2.15)	1.96 (1.63-3.13)	1.57 (1.37-2.00)	1.74 (1.61-1.95)	1.73 (1.52-2.15)
Duodenal ulcer (HP+) (n=17)	1.36 (1.20-1.60)	1.42 (1.22-1.58)	1.25 (1.10-1.44)	1.47 (1.32-1.66)	1.49 (1.24-1.69)
Duodenal ulcer (HP-) (n=2)	1.45 (1.40-1.50)	1.50 (1.40-1.60)	1.35 (1.20-1.50)	1.55 (1.40-1.70)	1.55 (1.50-1.60)

*p<0.01 or less, DU vs normal and gastritis for any time period; of 19 pH were excluded due to violation of the protocol resulting in 17 pH measurement.
†Total range.

TABLE III Area under the curve of the 24 hour pH profiles of normal subjects and of gastritis and duodenal ulcer patients

	Normal	Gastritis		Duodenal ulcer	
		HP (+)	HP (-)	HP (+)	HP (-)
Mean	2682	2643†	2712	2074*	2184
SD	527	485	622	555	550

*p<0.05, duodenal ulcer HP (+) v normal and all gastritis groups;
†not significant, gastritis HP (+) v gastritis HP (-) and normal subjects.

and that its eradication results in a lowering of the fasting and meal-bombesin stimulated gastrin concentration.^{6 9 11 14 28-30} However, the mechanism by which chronic infection of the gastric mucosa with *H pylori* results in increased gastrin is not known. Moreover, the consequences of *H pylori* associated hypergastrinaemia on gastric acidity are unknown.

It has recently been suggested by Levi *et al*⁶ that *H pylori* induced hypergastrinaemia may cause duodenal ulcer by an increase in gastric acid secretion. There are currently limited data relating gastric acidity to the presence of chronic *H pylori* infection. Levi *et al*⁶ reported that the basal and peak acid outputs in response to pentagastrin were higher in *H pylori* positive duodenal ulcer patients compared with *H pylori* negative patients. In contrast, Hui *et al* observed similar maximal acid output in *H pylori* positive and negative duodenal ulcer patients.³¹ Brady *et al* could not detect a constant relationship between *H pylori* and gastric acid secretion.⁷ Smith *et al* reported that there was no significant difference in the median integrated 24 intra-gastric acidity between *H pylori* positive and *H pylori* negative asymptomatic healthy subjects despite the presence of an inappropriate hypergastrinaemia.¹² Similarly, Goldschmiedt *et al* showed that in healthy humans *H pylori* infection was associated with hypergastrinaemia, but not with gastric acid hypersecretion.¹³

This is the first study which concurrently investigates 24 hour acidity and *H pylori* infection in gastritis and duodenal ulcer patients. In agreement with recent studies,^{12 13} our pH data show that gastric acidity is similar in subjects with normal gastric mucosa and in gastritis patients, whether or not they have *H pylori* infection. In this study, gastric acidity was assessed by ambulatory long term intragastric pH monitoring, this method ignores the volume of acid output. Smith *et al* measured gastric acidity using a gastric aspiration technique.¹² In contrast, Goldschmiedt *et al* determined the basal and stimulated acid secretion rate.¹³ Since the different acid measuring techniques all gave the same results, it is tempting to suggest that chronic *H pylori* infection does not affect gastric acid secretion despite the presence of hypergastrinaemia. However, it is possible that hypergastrinaemia has to persist for many years to induce an increase in the parietal cell mass which would then produce the hyperacidity characteristic of duodenal ulcer disease. This hypothesis cannot be clarified further in our study since patients with duodenal ulcer disease without *H pylori* infection were extremely rare. Our pH data from the two *H pylori* negative duodenal ulcer patients do not allow a definite conclusion.

Although there is accumulating evidence that *H pylori* infection is a major factor in the pathogenesis of duodenal ulcer disease, several questions regarding the putative link between gastric acidity and *H pylori* remain unresolved. Duodenal ulcer patients, as a group, secrete more acid than normal subjects, but more than half of duodenal ulcer patients have normal acid secretion.^{32 33} On the other hand, almost all duodenal ulcer patients have gastric *H pylori*

infection and one would therefore expect hyperacidity in almost all duodenal ulcer patients. The prevalence of *H pylori* infection increases with age, amounting to about 40% in whites in the fifth decade of life and about 70-80% in the eighth decade.³⁴ On the other hand, the lifetime prevalence of duodenal ulcer disease is less than 10%. If one assumes that *H pylori* associated hypergastrinaemia is responsible for the hyperacidity in duodenal ulcer disease, then the question of why most *H pylori* infected people do not develop hyperacidity or duodenal ulcer, or both, despite the presence of hypergastrinaemia arises. Finally, McColl *et al* did not observe a decrease in gastric acidity and gastric acid output seven months after eradication of *H pylori* in duodenal ulcer patients despite a sustained fall in gastrin.³⁵

In conclusion, our study shows that gastric acidity is similar in subjects with normal gastric mucosa and in *H pylori* positive and negative gastritis patients. Duodenal ulcer patients have increased gastric acidity. Based on these results, we assume that chronic *H pylori* infection does not change intragastric acidity in most infected subjects.

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