Influence of H. pylori infection on meal-stimulated gastric acid secretion and gastroesophageal acid reflux

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Feldman, Mark, Byron Cryer, Doug Sammer, Edward Lee, and Stuart J. Spechler. Influence of H. pylori infection on meal-stimulated gastric acid secretion and gastroesophageal acid reflux. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G1159–G1164, 1999.—Gastric acid secretion, gastrin release, gastric emptying, and gastroesophageal acid reflux were measured in asymptomatic individuals before and after elimination of Helicobacter pylori gastritis. After basal gastric acid secretion and serum gastrin concentrations were measured, meal-stimulated gastric acid secretion and gastrin release were assessed during in vivo intragastric titration to pH 3. Experiments were repeated 4 wk after treatment with lansoprazole, amoxicillin, and clarithromycin. Esophageal pH was also monitored for 24 h before and after therapy. Basal gastric acidity increased ~20 mmol/l in subjects whose infection was eradicated (P < 0.05) but not in those with persistent infection. Basal and meal-stimulated gastric acid secretion did not change after H. pylori eradication, despite a 41% reduction in meal-stimulated gastrin release (P < 0.05). Gastroesophageal acid reflux increased two- to threefold after successful treatment (P < 0.05) but did not change in subjects with persistent infection. Thus elimination of H. pylori gastritis increases gastric acidity, probably by reducing nonparietal alkaline secretion, and this may facilitate gastroesophageal acid reflux.

Helicobacter pylori

The majority of people who are infected with Helicobacter pylori are asymptomatic and have a gastritis involving the gastric body and antrum (2, 8, 9). Effects of H. pylori gastritis on gastric function are complex. H. pylori-associated antral gastritis typically leads to elevated circulating gastrin concentrations (5, 14). Because gastrin is the major physiological stimulant of gastric acid secretion after a meal (11), it is reasonable to predict that people with H. pylori gastritis would also have increased postprandial gastric acid secretion rates. However, studies performed nearly a decade ago in our laboratory demonstrated that meal-stimulated gastric acid secretion rates (measured by in vivo intragastric titration to pH 5) were nearly identical in seropositive and seronegative individuals, even though the seropositive individuals had twofold higher postprandial circulating gastrin levels (14). Maintaining intragastric pH at a constant level after the meal was critical from an experimental standpoint, because gastrin release is markedly influenced by gastric pH and vice versa (7). In retrospect, however, because intragastric pH after a meal normally ranges from 1.5 to 4.5 (7), a controlled intragastric pH of 5 may not have been the most physiological pH level at which to study the role of H. pylori infection on meal-stimulated acid secretion and gastrin release.

Effects of H. pylori on meal-stimulated gastric acid secretion and gastrin release can be examined more directly by studying individuals before and after eradication of H. pylori gastritis. Therefore, in the present study of asymptomatic individuals with H. pylori gastritis, we measured meal-stimulated gastric acid secretion and gastrin release at a more physiological intragastric pH of 3, and we repeated the experiments 4 wk after completing a 2-wk course of therapy with lansoprazole, amoxicillin, and clarithromycin designed to eliminate the gastritis. Basal gastric acidity and acid output were also measured just prior to each meal study. Gastric biopsies from the gastric body and antrum were obtained at the completion of the gastric secretory study, both before and after therapy, to determine whether the gastritis was eliminated.

We also investigated whether elimination of H. pylori gastritis would increase gastroesophageal acid reflux as assessed by ambulatory 24-h esophageal pH monitoring. We performed these additional esophageal pH experiments because clinical and epidemiologic studies suggest that eradication of H. pylori (or its absence) increases the incidence of reflux esophagitis (17, 20, 21). The effect of H. pylori eradication on postprandial gastric emptying of polyethylene glycol (PEG) was also assessed.

METHODS

Subjects

Asymptomatic subjects with no history of duodenal ulcer, gastric ulcer, reflux esophagitis, gastric cancer, gastric surgery, or prior treatment of H. pylori gastritis underwent serologic testing for IgG antibodies to H. pylori as described previously (8). The first 25 subjects who were seropositive participated. None was receiving gastric antisecretory drugs. One woman who secreted no acid on the baseline study (see below) was excluded from further participation. Ages of the 12 other women and of the 12 men ranged from 28 to 54 yr (median 41 yr). Seventeen were African American, four were Caucasian, and three were Hispanic. Their weights ranged from 57 to 136 kg (median 91 kg). Studies were approved by a human studies subcommittee of our medical center research committee. Informed written consent was obtained from each participant.

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Baseline Studies

Intubation. After an overnight fast, subjects swallowed a 16-F gastric tube (Anderson, Oyster Bay, NY), the tip of which had been cut open to allow forceps to be passed through it at the end of the 3-h secretion experiment to obtain gastric mucosal biopsies (see below). This modification of the tube does not interfere with the high (>90%) recovery of gastric juice that occurs when the tip of the gastric tube is positioned in the distal stomach under fluoroscopic guidance (2). After gastric intubation, all gastric juice present after the overnight fast was removed from the stomach by manual aspiration. The pH of this residual gastric juice was determined with a glass electrode and converted to acidity (H⁺ concentration in mmol/l) (18).

Basal secretion. Basal acid output (BAO) was then measured by aspirating fasting gastric secretions for 15 min periods. The volume of each 15-min aliquot (in liters) was multiplied by its acidity (mmol/l) to calculate each 15-min acid output (mmol H⁺/15 min). BAO was calculated as the sum of the four 15-min outputs (mmol/H). At the beginning and at the end of the 60-min BAO collection, blood samples for fasting serum gastrin measurement (15) were obtained from an indwelling venous catheter.

Meal-stimulated secretion. Next, a 600-ml homogenized steak meal that was adjusted to pH 3.0 with 0.1 N HCl and that contained 6 g of the nonabsorbable marker PEG was infused into the stomach by gravity through the gastric tube. Gastric acid secretion in response to the meal was measured for 120 min by in vivo intragastric titration to pH 3.0, using 0.3 N NaHCO₃ as the titrant. The number of millimoles of NaHCO₃ required to maintain intragastric pH at 3.0 is multiplied by its acidity (mmol/l) to calculate each 15-min period. The volume of each 15-min aliquot (in liters) was multiplied by its acidity (mmol/l) to calculate each 15-min acid output (mmol H⁺/15 min). BAO was calculated as the sum of the four 15-min outputs (mmol/H). At the beginning and at the end of the 60-min BAO collection, blood samples for fasting serum gastrin measurement (15) were obtained from an indwelling venous catheter.

Gastric emptying. The stomach was emptied by aspiration 120 min after the meal, and the volume (liters) of gastric fluid was recorded. The stomach was then rinsed quickly with 0.1 liter isotonic saline. PEG concentrations of the gastric contents that were aspirated at 120 min and of the saline rinse fluid were measured turbidimetrically (16). PEG concentrations (g/l) were multiplied by the volumes of fluid aspirated (liters), and the products (g) were subtracted from the amount of PEG added to the original meal (6 g). The actual PEG content of the meal was determined by multiplying the measured PEG concentration of the meal by its volume (0.6 liter). The difference between the amount of PEG in the meal and the amount of PEG remaining in the stomach represented the amount of PEG that had emptied after 120 min, and this amount was expressed as a percentage of the amount of PEG added to the meal.

Gastric mucosal biopsies. After the stomach contents had been aspirated, three mucosal biopsies from the gastric antrum and two from the gastric body were obtained under fluoroscopic guidance by passing an endoscopic biopsy forceps through the tip of the modified gastric tube (2). One biopsy from the antrum was used for rapid urease testing for H. pylori (CLO test; Tri-Med Specialists, Lenexa, KS). Remaining antral and body biopsies were coded, placed in fixative, and stained with hematoxylin and eosin. One of us (E. Lee), who had no clinical information, then verified the location of the biopsy (antral mucosa, body mucosa), the presence or absence of H. pylori, and the presence or absence of chronic gastritis (2, 8, 9). Gastritis, if present, was graded for severity as none (a score of 0), mild (1), moderate (2), or severe (3), as described previously (2, 8, 9).

Ambulatory esophageal pH monitoring for 24 h. After completion of the 3-h baseline gastric secretory and biopsy studies previously described, 15 subjects (7 men, 8 women) consented to undergo 24-h ambulatory esophageal pH monitoring on a separate day. The other nine subjects, although willing to undergo the 3-h gastric secretion studies in our laboratory, were unwilling to allow a nasoesophageal tube to be in place for 24 h.

After an overnight fast, a solid-state manometry catheter (Synectics Medical, Irving TX) was passed through the nose into the stomach. The manometry catheter was connected to a personal computer Polygraf data acquisition device, and the digital information provided was analyzed using Polygram function testing software (Gastrosoft). The lower esophageal sphincter (LES) was identified using the station pull-through technique, and the distance from the nares to the proximal extent of the LES was recorded. After removal of the manometry catheter, an antimony pH catheter using an external reference electrode (Synectics Medical) was passed through the nose and positioned so that the sensor was located 5 cm above the proximal level of the LES (as determined by the esophageal manometry catheter). The pH electrode was connected to a portable data recorder (Digitrapper Mk III; Synectics Medical) for ambulatory 24-h esophageal pH monitoring. Subjects were instructed to keep a diary to record the time of meals and the foods ingested during the monitoring period. Computerized esophageal pH data were analyzed using Esophagram Reflux Analysis software (Gastrosoft). During the repeat study, subjects were instructed to eat the same foods at the same time as those recorded in the diary for the first study. The pH electrode was positioned at the same level as in the original study. The percent of the monitoring period in which the esophageal pH was <4.0 was determined.

Antimicrobial Therapy and Posttherapy Studies

The day after completion of the baseline studies described, each subject received 30 mg lansoprazole, 1 g amoxicillin, and 500 mg darithromycin (LAC) twice daily for the next 14 days. This regimen is approved for H. pylori eradication (19). Four weeks after completion of LAC, all 24 subjects had another 3-h fasting and meal-stimulated gastric secretion study, with serum gastrin and gastric emptying measurements, after which all were rebiopsied as previously described. H. pylori was considered eliminated if tissue stains from both the gastric body and antrum 4 wk after completion of LAC were negative for the organism and if the rapid urease test reverted from positive to negative. H. pylori infection was considered persistent if one or both biopsies continued to show H. pylori organisms and/or if the rapid urease test remained positive. Ambulatory 24-h esophageal pH monitoring was also repeated in 14 of the 15 subjects who had consented to a baseline 24-h ambulatory pH study; 1 subject refused to undergo the posttreatment ambulatory pH study.

Statistical Analyses

Subjects were divided into two groups (infection eliminated, infection persistent) based on their final H. pylori status (see above). In each group, paired t-tests (2-tailed) were used to compare before vs. after data if the data appeared to be normally distributed; these data are presented as means ± SE. Wilcoxon’s tests (2-tailed) were used if the data appeared to be not normally distributed; these data are presented as medians. In some cases, both tests were used (see Results). P < 0.05 was considered significant. Data were
managed and analyzed using Systat 6.0.1 for Windows (SPSS, Chicago, IL).

RESULTS

Elimination of *H. pylori* Infection by LAC and Resultant Changes in Gastric Histology

Gastric biopsies were positive for *H. pylori* by tissue stain and rapid urease test in all 24 subjects at baseline. Gastritis was typically present in both the gastric body and antrum (pangastritis; Fig. 1). The 14-day course of LAC was successful in eradicating *H. pylori* in 16 subjects (67%; 95% confidence interval: 46%, 87%). As shown in Fig. 1A, elimination of *H. pylori* was associated with resolution of gastritis in both the gastric body and antrum (P < 0.001).

In eight subjects *H. pylori* remained visible on tissue stain and in seven of the eight the rapid urease test remained positive 4 wk after completion of LAC. Persistent *H. pylori* infection was associated with persistent gastritis in the gastric body and antrum (Fig. 1B).

Serum Gastrin Concentrations

There were no significant changes in average fasting serum gastrin concentrations from baseline 4 wk after LAC either in subjects whose infection was eliminated (41 ± 4 pg/ml before treatment vs. 39 ± 5 pg/ml after LAC; P = 0.45) or in subjects whose infection persisted (37 ± 8 pg/ml before treatment vs. 44 ± 7 pg/ml after LAC; P = 0.10). In contrast, as shown in Fig. 2A, there was a 41% decrease in the integrated gastrin response to the meal in subjects whose infection was eliminated (P = 0.01). There was no significant change in postprandial gastrin release in subjects whose *H. pylori* infection persisted (Fig. 2B; P = 0.82).

Gastric Secretion

Basal gastric juice acidity and volume output. In subjects whose *H. pylori* infection was eliminated, residual gastric juice acidity nearly doubled, from 21.0 ± 6.3 mmol/l before therapy to 40.2 ± 9.7 mmol/l after LAC (P = 0.02). On the other hand, in subjects whose *H. pylori* infection was not eradicated, there was a small, insignificant increase in residual gastric juice acidity (12.8 ± 4.2 mmol/l before treatment vs. 17.9 ± 8.2 mmol/l after LAC; P = 0.40).

During the 1-h basal collection, average gastric acidity was also nearly 20 mmol/l higher after *H. pylori* infection was eliminated compared with at baseline (P = 0.004). Basal acidity did not increase significantly in subjects whose *H. pylori* infection was not eliminated. Basal gastric juice volume output decreased from 106.4 ± 9.6 to 82.9 ± 11.3 ml/h in subjects whose infection was eliminated (P = 0.10). Such a trend was not evident in individuals whose infection persisted.
Meal-stimulated gastric acid secretion. Four weeks after completion of LAC, there were no significant changes in meal-stimulated acid secretion either in subjects whose H. pylori infection was eliminated or in subjects whose infection was not eliminated. In the former group, meal-stimulated acid secretion averaged 12.0 ± 2.4 mmol/h before treatment and 11.7 ± 2.0 mmol/h after LAC. In the latter group, acid secretion averaged 11.6 ± 1.4 mmol/h before treatment and 11.3 ± 1.6 mmol/h after LAC.

Figure 3 plots means ± SE BAO and meal-stimulated acid secretion in the two groups, both before treatment and 4 wk after completion of LAC.

Gastrointestinal Acid Reflux; 24-h Ambulatory pH Monitoring

Acid reflux increased significantly in subjects whose H. pylori infection was eliminated. Reflux occurred during 2.0% of the monitoring period before treatment (median) as opposed to 3.9% of the monitoring period after LAC (P = 0.04). Mean reflux values were 1.9 ± 0.6% before therapy and 5.6 ± 1.6% after LAC (P = 0.03). Mean basal gastric acidity also increased nearly 20 mmol/l after LAC in these nine subjects.

Acid reflux increased in seven of nine individuals after elimination of H. pylori gastritis (Fig. 4). However, pathological acid reflux (>6% esophageal acid exposure) developed in only three of the nine subjects.

In subjects whose H. pylori infection was not eliminated by LAC, acid reflux did not change significantly (median reflux 1.2% of the monitoring period before treatment vs. 0% after LAC; P = 0.72; mean reflux 1.3 ± 0.6% before therapy vs. 3.6 ± 3.2% after LAC, P = 0.55). Likewise, basal gastric acidity did not change significantly in the five subjects with persistent gastritis. Pathological acid reflux developed in one subject (Fig. 4).

**DISCUSSION**

The most accurate method to measure gastric acid secretion with food in the stomach is the in vivo intragastric titration technique of Fordtran and Walsh (12), a method that is valid at any pH between 2.5 and 5.5. This is the first study to evaluate the effect of elimination of H. pylori gastritis on meal-stimulated gastric acid secretion. A previous cohort study by Goldschmiedt et al. (14), using in vivo titration to pH 5, reported similar gastric acid secretion rates in H. pylori seropositive and seronegative subjects, despite twofold higher gastrin levels in the infected group. In the present study, in which in vivo intragastric titration...
was performed at a more physiological pH of 3, we found no change in meal-stimulated acid secretion after elimination of *H. pylori*, despite a nearly 50% reduction in the gastrin response to the meal after *H. pylori* eradication.

Failure of meal-stimulated acid secretion to decline in parallel with gastrin release after cure of *H. pylori* pangastritis could be the result of a gastric body mucosa that is now healthier and more responsive to stimulation by lower amounts of gastrin. However, the acid secretory responsiveness to circulating human gastrin-17 is nearly identical in *H. pylori*-positive and -negative individuals (14). Thus other explanations for the disparity in our meal-stimulated gastrin and acid secretion results need to be considered.

During in vivo intragastric titration, exogenous bicarbonate is infused into the stomach at a rate sufficient to titrate secreted acid (12). However, the stomach also secretes bicarbonate (6). Thus the measurement of meal-stimulated gastric acid secretion rates by in vivo intragastric titration with exogenous sodium bicarbonate actually detects net acid secretion in response to the meal (acid secretion minus endogenous bicarbonate secretion). Entry of bicarbonate into the gastric lumen decreases after elimination of *H. pylori* gastritis (8), either due to less gastric bicarbonate secretion or to less exudation of alkaline fluid through the no longer inflamed gastric mucosa. A reduction in gastric bicarbonate is the likely mechanism for increased gastric acidity after *H. pylori* eradication (see below). As a consequence of reduced endogenous bicarbonate secretion, one might have anticipated a higher requirement for sodium bicarbonate titrant use in our meal studies after eradication of *H. pylori* infection, giving the appearance of increased gastric acid secretion. That net postprandial gastric acid secretion (as assessed by in vivo titration with exogenous sodium bicarbonate) did not increase in this study after cure of *H. pylori* gastritis is probably the result of less postprandial gastrin release and less gastrin-driven postprandial acid secretion. In other words, elimination of *H. pylori* gastritis may reduce postprandial gastric acid and bicarbonate secretion more or less equally, with no change in net acid secretion as assessed by in vivo intragastric titration.

Previous studies in humans have used intravenous infusion of the neural peptide gastrin-releasing peptide (GRP) in high doses to evaluate endogenous gastrin release before and after elimination of *H. pylori* infection. These studies have shown marked reductions in GRP-stimulated gastrin release (4, 5). However, intravenous GRP is not a physiological stimulant of gastrin release, and the pH within the stomach was not controlled in those prior experiments. When we kept the gastric pH constant by in vivo titration to pH 3, elimination of *H. pylori* gastritis lowered gastrin release induced by a meal by more than 40%. In contrast, failure to eliminate *H. pylori* gastritis had no effect on meal-stimulated serum gastrin levels. Presumably, resolution of antral inflammation reduces stimulation of antral G cells by cytokines or restores the inhibitory effect of antral D (somatostatin) cells on antral G cells.

After eradication of *H. pylori* in duodenal ulcer patients in one study, the incidence of reflux esophagitis increased twofold, which the authors attributed to weight gain (17). Other studies have shown a correlation between reflux esophagitis and the absence of *H. pylori* infection (20, 21). These clinical and epidemiologic observations raise the intriguing possibility that eradication of *H. pylori* gastritis (or its absence) may somehow facilitate acid reflux (1). In the present experiment, 24-h gastroesophageal acid reflux increased in nearly 80% of subjects 4 wk after cure of *H. pylori* gastritis, whereas acid reflux increased in only 20% of subjects after unsuccessful treatment. Pathological acid reflux developed in 4 of 14 subjects after antimicrobial therapy, in 3 after successful therapy and in 1 after unsuccessful therapy. Because only 14 subjects participated in both of our two 24-h esophageal pH experiments, additional studies in larger groups of individuals are necessary to confirm these findings.

Acid reflux after elimination of *H. pylori* infection did not appear to be a consequence of delayed gastric emptying or increased gastric volume. However, our studies do suggest a mechanism for reflux after elimination of *H. pylori* gastritis, namely the increase in fasting (basal) gastric acidity, which was observed in this study and in previous ones using different regimens to eradicate *H. pylori* (3, 8, 22). Whether elimination of *H. pylori* gastritis would have a direct inhibitory effect on basal LES function or on the frequency of transient relaxations of the LES is uncertain.

It is possible that the significant, nearly 20 mmol/l, increase in basal gastric acidity we observed occurred as a consequence of earlier therapy with the proton pump inhibitor lansoprazole (i.e., an acid rebound effect) (13), but this seems unlikely for three reasons. First, both eradicated and noneradicated subjects were exposed to lansoprazole, yet basal gastric acidity increased significantly only if gastritis was eliminated. Second, gastric acidity measurements were repeated a full 4 wk after the last dose of lansoprazole, although it is conceivable that an acid rebound effect could last this long. Third, increases in gastric acidity after elimination of *H. pylori* have also been seen in earlier studies, which did not employ a proton pump inhibitor or any other acid antisecretory drug to help eradicate *H. pylori* (3, 8, 22). One of these studies also demonstrated that the increase in gastric acidity after *H. pylori* eradication could not be explained by less gastric ammonia production consequent to loss of *H. pylori* urease (22).

In a recent study, we demonstrated that the increase in fasting gastric acidity after *H. pylori* eradication is not caused by more H⁺ secretion from parietal cells but instead is a consequence of less secretion of alkaline fluid from nonparietal cells (8). Because basal nonparietal gastric secretion contains water and bicarbonate (6, 7), a reduction in nonparietal secretion after *H. pylori* eradication would raise basal gastric juice acidity because of less dilution and less neutralization of H⁺, even if the number of H⁺ secreted by parietal cells...
is constant. Our observation that total gastric juice volume (parietal plus nonparietal) declined more in subjects whose infection was eliminated than in subjects whose infection persisted (by 24 vs. 6 ml/h) supports lower nonparietal secretion as a mechanism for increased gastric acidity after Helicobacter pylori eradication.

In summary, this experiment in asymptomatic men and women with H. pylori-associated pangastritis demonstrated that elimination of gastritis increases fasting gastric acidity without significantly changing basal or meal-stimulated gastric acid secretion rates. The increased acidity is probably a consequence of reduced secretion, or exudation, of alkaline nonparietal fluid into the gastric lumen. The increased gastric acidity after cure of H. pylori pangastritis is associated with (and could even be the cause of) increased gastroesophageal acid reflux. Whether acid reflux would increase in other populations treated for H. pylori infection (e.g., duodenal ulcer patients) is uncertain, although clinical-endoscopic trials suggest that this would be the case (17).

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