**Gastric acid secretory response in Helicobacter pylori-positive patients with duodenal ulcer disease**

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**BACKGROUND:** Patients with duodenal ulcer (DU) have an increased parietal cell mass and sensitivity to secretagogues, with increased acid output.

**AIM:** To determine the effect of Helicobacter pylori eradication on parietal cell sensitivity and gastric acid secretion.

**SUBJECTS AND METHODS:** Twenty-five H pylori-positive DU patients and 18 H pylori-negative healthy volunteers were studied. Serum H pylori immunoglobulin G, basal acid output and acid secretory response to graded doses of pentagastrin were determined before and after treatment, at six months and at one year. Subjects were randomly assigned to ranitidine or sucralfate treatment for six weeks, and all DU patients received bismuth subsalicylate, metronidazole and tetracycline for the first two weeks.

**RESULTS:** H pylori was eradicated in 66% of patients receiving sucralfate and 92% receiving ranitidine. Compared with healthy volunteers, DU patients demonstrated a 2.7-fold greater basal acid output, a 1.3-fold greater peak acid output, significantly higher acid output for each dose of pentagastrin and a 1.38-fold increase in the area under the pentagastrin dose acid response curve. Cure of H pylori, irrespective of ulcer healing regimen, resulted in a gradual decrease in acid secretory capacity with basal acid output, peak acid output and area under the pentagastrin dose acid response curve returning to healthy volunteer levels by one year. No demonstrable differences were observed in parietal cell sensitivity in all subjects before or after treatment. These data suggest that disturbances in acid secretion in H pylori-positive DU patients are not due to an increased parietal cell sensitivity to pentagastrin but rather due to an increased parietal cell mass with increased capacity to secrete acid, which gradually resolves following cure.

**Key Words:** Duodenal ulcer; Gastric acid secretion; Helicobacter pylori

Réaction sécrétoire de l’acide gastrique chez les patients porteurs d’Helicobacter pylori qui souffrent d’un ulcère gastro-duodénal

**CONTEXTE :** Les patients souffrant d’un ulcère gastro-duodénal (UGD) présentent une masse plus importante de cellules pariétales et une sensibilité accrue aux sécrétagogues, accompagnées d’une augmentation de la production acide.

**OBJECTIF :** Déterminer l’effet de l’éradication d’Helicobacter pylori sur la sensibilité des cellules pariétales et la sécrétion acide gastrique.

**SUJETS ET MÉTHODE :** Vingt-cinq patients porteurs d’H. pylori souffrant d’un UGD et 18 sujets volontaires, exempts d’H. pylori, en bonne santé, ont participé à l’étude. On a mesuré le taux d’immunoglobulines G sériques contre H. pylori, la sécrétion acide basale et la réaction de la sécrétion acide à des doses graduées de pentagastrine avant et après le traitement, après six mois et au bout d’un an. Les sujets ont été dirigés au hasard vers le traitement à la ranitidine ou au sucralfate d’une durée de six semaines, et tous les patients atteints d’un UGD ont reçu du subsalicylate de bismuth, du métronidazole et de la tetracycline pendant les deux premières semaines.

**RÉSULTATS :** H. pylori a été éradiqué chez 66 % des patients traités au sucralfate et chez 92 % des patients traités à la ranitidine. Comparativement aux sujets volontaires en santé, les patients souffrant d’un UGD présentaient...
The relationship between *Helicobacter pylori* infection and duodenal ulcer (DU) disease is well established. *H pylori* infection is documented in up to 95% of patients with DU and is associated with an increase in gastric acid secretion. Although acid suppression results in healing of DU, eradication of infection is required to prevent ulcer recurrence (1-5). The exact mechanisms by which *H pylori* predisposes patients to DU remain to be determined.

It has long been recognized that patients with DU have an increased parietal cell mass, resulting in an increased maximal acid-secretory capacity (6,7). Parietal cell hyperplasia is seen after treatment with gastrin (8) as well as pentagastrin (9), suggesting that the hypergastrinemia associated with *H pylori* infection (10-13) is responsible for the increased parietal cell mass in patients with DU. Furthermore, some studies have demonstrated that DU patients have an increased parietal cell sensitivity to secretagogues (14-16). Thus, the increased capacity and responsiveness of the parietal cells to secrete acid (17), together with the impaired inhibitory control mechanisms on acid secretion, including a reduced somatostatin concentration in the gastric mucosa (18,19), lead to acid hypersecretion in patients with DU.

Several studies have suggested that the acid secretory responses following ulcer healing vary according to the therapeutic agent used. These studies have demonstrated that the acid secretory response and parietal cell sensitivity decrease with DU healing following treatment with sucralfate but remain essentially unchanged following ulcer treatment with ranitidine (20-23). The observed failure of ranitidine to decrease the secretory responses has been attributed to altered receptor regulation and/or acid rebound, which has been documented both in healthy volunteers and in subjects with healed DU following treatment with *H2*-receptor antagonists (24-27). Whether this effect is simply due to an increase in parietal cell mass, to an increase in *H2*-receptor sensitivity or to a true biological *H2*-receptor upregulation is unclear.

In the present study, we aimed to determine whether cure of *H pylori* infection leads to a decrease in parietal cell mass and sensitivity to pentagastrin, and examine the influence of different ulcer treatments. *H pylori* infection was treated with bismuth-based triple therapy plus either sucralfate or ranitidine, which was standard therapy at the time of commencement of the study. Parietal cell mass was measured by peak acid output (PAO), and parietal cell sensitivity measured by the median effective dose (ED50) in response to pentagastrin.

PATIENTS AND METHODS

**Subjects studied:** Twenty-seven patients – 26 male and one female – with uncomplicated DU disease were recruited at McMaster University Medical Centre, Hamilton, Ontario, between 1991 and 1995. For each patient, a DU was documented endoscopically within one year of commencement of the study. Ten patients were smokers. *H pylori* status was confirmed by serology, histology and culture of antral and body biopsies. Twelve patients had an active DU, and one patient also had a prepyloric ulcer at the start of the study. None of the patients were taking an *H2*-receptor antagonist, omeprazole, bismuth compound or antibiotics within four weeks of commencement of the study. In addition, none of the patients were on nonsteroidal anti-inflammatory drugs; however, one patient with polycythemia rubra vera who was on acetylsalicylic acid at the time of inclusion was maintained on acetylsalicylic acid (Table 1). Eighteen *H pylori*-negative healthy male volunteers with no prior history of peptic ulcer disease were recruited through local advertisements within the catchment area of the hospital and were also studied. None of the volunteers were taking any medication at the time of study. *H pylori* status was determined in the same manner as with the DU patients. Individuals with a known allergy to study drugs or related products were excluded. Other exclusion criteria included any contraindication to oral or nasal intubation required for endoscopy or secretory tests.

This study was designed in accordance with the declaration of Helsinki/Tokyo and approved by the Research Advisory Committee of the McMaster University Medical Centre. Written informed consent was obtained from all participants before commencement of the study.

**Study design:** Before inclusion in the study, patients and volunteers underwent screening by medical history, physical examination and routine blood work including *H pylori* serology and urinalysis. All subjects underwent upper gastrointestinal endoscopy followed by acid secretory studies.

Investigations were repeated in study subjects at six weeks, and only in the *H pylori*-positive patients at six months and 12 months after commencement of the study. Patients who failed initial cure were retreated, then restudied six weeks later, and at six months and one year after cure. **Endoscopy and biopsy:** At endoscopy, four biopsies were taken from the antrum (5 cm from the pylorus on the greater curve) and two from the body (5 cm from the gastroesophageal junction on the greater curve) for histological examination.
Acid secretion response: Basal acid output (BAO) was determined by taking the gastric juice collected over the second 30 min basal period and expressed as mmol/30 min. PAO was determined by taking the highest acid output over a 30 min period in response to one dose of pentagastrin and expressed as mmol/30 min. The pentagastrin dose-response data for each patient were analyzed and the area under the curve (AUCP) calculated and expressed as mmol. In addition, the apparent parietal cell sensitivity (D50) and intrinsic parietal cell sensitivity (Km) were determined as previously described by Hirschowitz (29), using an exponential model,

\[ V = V_{\text{max}} (1 - e^{-bD}) \]

where \( V = \text{output} \) and \( D = \text{dose of pentagastrin} \). From this analysis, we obtained the threshold dose:

\[ T = \frac{c}{b} \]

\[ K_c = \ln \frac{2}{b} \]

\[ D_{50} = \frac{K_c}{e^{T}} - T \]

D50 is the dose of pentagastrin required to raise the output from basal to 50% of the calculated maximum output (Vmax) and is an index of apparent sensitivity. Kc is a measure of intrinsic sensitivity and is the dose of pentagastrin needed to raise the output to 50% of Vmax, assuming that the basal output was zero.

Serology: Serology was determined using a standard Pylori Stat test kit (ELISA for H pylori immunoglobulin [Ig] G antibody in human serum; BioWhittaker Inc, USA). With this kit, serum samples were tested concomitantly with three standards and two serum controls. Labelled index values for each standard were provided for linear regression analysis of test results. Control serum samples with predicted index values were used to confirm test validity. The results are expressed as absorbance, and an optical density of 0.80 was
TABLE 2
Patient characteristics, drug treatment and Helicobacter pylori status after treatment with sucralfate or rinitidine

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Sex</th>
<th>Age range (years)</th>
<th>Weight (kg) mean ± SEM</th>
<th>Rx</th>
<th>H pylori eradication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H pylori-positive patients with</td>
<td>24</td>
<td>Male (96%)</td>
<td>19-67</td>
<td>82.71±4.18</td>
<td>12</td>
<td>8 (66%)</td>
</tr>
<tr>
<td>duodenal ulcer</td>
<td>1</td>
<td>Female (4%)</td>
<td></td>
<td></td>
<td>13</td>
<td>12 (92%)*</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>18</td>
<td>Male (100%)</td>
<td>20-42</td>
<td>79.75±3.36</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>–</td>
</tr>
</tbody>
</table>

*H pylori eradication 6/52 patients after commencement of study (4/52 after triple regimen); † P=0.05 compared with eradication rate achieved with sucralfate

**Figure 1** Basal acid output (BAO) in healthy volunteers (HV) before treatment (Pre Rx) and after treatment (Post Rx) and in Helicobacter pylori-positive patients with duodenal ulcer (DU) disease Pre Rx, and one month, six months and one year Post Rx. Compared with HV, Pre Rx BAO increased in DU patients (P=0.03). In HV Post Rx, BAO increased over Pre Rx levels (P=0.02), and in DU patients BAO decreased Post Rx but failed to reach significance over Pre Rx levels by one year (P=0.29). ● H pylori-positive patients cured with one course of eradication therapy. ▲ H pylori-positive patients requiring a second course of eradication therapy

Defined as seronegative, 0.80 to 0.99 as equivocal and 0.99 as seropositive.

**Eradication of H pylori infection**: Following the initial endoscopy and acid secretory study, all subjects were randomly assigned by a computer-generated randomization code to receive a six-week course of either sucralfate 1 g qid or rani-
tidine 300 mg per day at bedtime. In addition, the H pylori-positive DU patients also received metronidazole 500 mg tid and tetracycline 500 mg qid for the first week and bismuth subsalicylate one tablet qid for the first two weeks. Compliance was assessed by pill counting at follow-up, and any adverse events were documented in the case study books.

Following the six-week course of therapy, patients who initially failed to cure H pylori were retreated with what was considered to be the most effective therapy at the time (ome-prazole and amoxicillin for two weeks).

**Statistics**: Each patient acted as their own control, and group comparisons were made between patients and healthy volunteers before and after treatment, and with patients before and after treatment, and at six months and one year. Statistical analysis was performed using the Wilcoxon Signed Rank test for paired data and the Mann-Whitney test for unpaired data. ANOVA was used to compare the dose-response curves between groups. P=0.05 was considered significant.

**RESULTS**

Of the 27 patients recruited to the study, two patients who were randomly assigned to the ranitidine arm of treatment were excluded. One patient was subsequently shown to be H pylori negative before treatment, and the second patient refused any post-treatment investigation because he felt so well. Two additional patients, one in each of the treatment arms, refused acid secretory studies but underwent all other investigations. The patient in the ranitidine arm was H pylori negative, and the patient in the sucralfate arm was H pylori positive after treatment. The clinical characteristics of the study population are shown in Tables 1 and 2. All healthy volunteers were compliant with their medication, whereas compliance could only be verified in 20 subjects in the patient population. The remaining five individuals failed to return either their pill boxes or compliance cards; however, all otherwise indicated compliance at interview. Three of these patients were H pylori negative after treatment, and two remained H pylori positive and required a second course of eradication therapy. All patients were included in the analysis.

H pylori eradication was achieved in 20 of 25 (80%) infected patients (Table 2). Of the 13 patients with an active ulcer, healing was demonstrated in all but one patient who required a second course of therapy before confirmed healing. Ranitidine plus triple therapy achieved an eradication rate of 92%, whereas sucralfate plus triple therapy achieved eradication in 66% (P=0.05). In general, the medications were well tolerated, with 11 patients complaining of mostly mild, short-lived symptoms occurring predominantly during antibiotic use and settling rapidly thereafter. One patient in the sucralfate group required a course of nystatin for oral thrush, and a second patient in the ranitidine group required a two-week course of metronidazole (500 mg tid) for diarrhea secondary to Clostridium difficile. Three volunteers complained of mild abdominal discomfort during the first week of therapy.

**Figure 1** Basal acid output (BAO) in healthy volunteers (HV) before treatment (Pre Rx) and after treatment (Post Rx) and in Helicobacter pylori-positive patients with duodenal ulcer (DU) disease Pre Rx, and one month, six months and one year Post Rx. Compared with HV, Pre Rx BAO increased in DU patients (P=0.03). In HV Post Rx, BAO increased over Pre Rx levels (P=0.02), and in DU patients BAO decreased Post Rx but failed to reach significance over Pre Rx levels by one year (P=0.29). ● H pylori-positive patients cured with one course of eradication therapy. ▲ H pylori-positive patients requiring a second course of eradication therapy

H pylori eradication 6/52 patients after commencement of study (4/52 after triple regimen); † P=0.05 compared with eradication rate achieved with sucralfate

**Short term acid secretory response before and after H pylori eradication**: H pylori-positive patients (n=25, Table 2) demonstrated a significantly higher mean BAO than healthy volunteers (n=18; P=0.03; Figure 1, Table 3). The
Acid output to each graded dose of pentagastrin was significantly higher than in healthy volunteer levels (P<0.01; Figure 2). Furthermore, H pylori-positive patients showed significantly higher mean PAO (P<0.01; Figure 3, Table 3) and AUCp (P=0.02; Figure 4, Table 3).

Treatment of all patients (n=23; Table 2) was associated with minimal change in BAO (Figure 1, Table 3), PAO (Figure 3, Table 3), AUCp (Figure 4, Table 3) and shift in the dose-response curve (Figure 2). However, when patients were separated into those who were cured by initial therapy (n=20) and those who were not (n=5), differences in pre-treatment acid secretory responses were seen (Figure 5, left).

Cure of H pylori infection four weeks after triple therapy (n=19; Tables 1 and 2) was associated with a decrease in BAO (Figure 1), PAO (Figure 3) and AUCp (Figure 4), and a shift in the dose-response curve to the right (Figure 3, right). However, the decrease in these parameters failed to reach significance over pretreatment levels. Moreover, the acid output to each graded dose of pentagastrin remained significantly higher than healthy volunteer post-treatment levels (P<0.01; Figure 5). No significant differences were noted between patients treated with ranitidine and those treated with sucralfate.

**TABLE 3**

<table>
<thead>
<tr>
<th>Acid output</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Sixmonths after treatment</th>
<th>One year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HV (18)</td>
<td>DU (25)</td>
<td>DU (23)</td>
<td>DU (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAO</td>
<td>2.6±0.6</td>
<td>6.9±1.3*</td>
<td>4.7±1.0†</td>
<td>5.6±1.2†</td>
</tr>
<tr>
<td>PAO</td>
<td>32.1±1.9</td>
<td>43.4±2.7‡</td>
<td>33.7±2.1†</td>
<td>42.0±2.9‡</td>
</tr>
<tr>
<td>AUCp</td>
<td>137.2±9.3</td>
<td>195.8±15.9‡‡</td>
<td>145.8±10.8§§</td>
<td>189.9±14.6††</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM. There were no significant differences for the following comparisons: DU after treatment versus DU before treatment; DU six months after treatment versus DU before treatment; DU one year after treatment versus HV before treatment. *P=0.03 HV versus DU before treatment; †Ranitidine increased the basal acid output/30 min (BAO) (P=0.02) in HV after treatment versus HV before treatment, whereas sucralfate had no effect; ‡P=0.01 DU after treatment versus HV before treatment; ‡‡P=0.02 DU six months after treatment versus HV before treatment; §P=0.01 HV versus DU before treatment; ¶P=0.01 DU one year after treatment versus DU before treatment; ¶¶P=0.02 HV versus DU before treatment; ††Ranitidine increased the area under the pentagastrin dose acid response curve (AUCp) (P=0.02) in HV after treatment versus HV before treatment, whereas sucralfate had no effect; †††P=0.01 DU after treatment versus HV before treatment; ††††P=0.03 DU six months after treatment versus HV before treatment; †††††P=0.05 DU one year after treatment versus DU before treatment. PAO Highest acid output/30 mins.
with sucralfate, with the exception that patients treated with sucralfate showed a 45% decrease in BAO (P=0.04), whereas, with ranitidine treatment, the BAO remained essentially unchanged.

H pylori-positive patients who remained infected (n=5) demonstrated higher pretreatment acid output for the secretory parameters measured than patients who achieved initial cure, and these parameters remained unchanged with treatment (n=4; Figures 1, 3, 4, 5).

In healthy volunteers, sucralfate treatment had no effect on any of the acid secretory parameters measured, whereas ranitidine treatment resulted in a significant increase in both BAO (P=0.02; Figure 1, Table 3) and AUCp (P=0.02; Figure 4, Table 3).

Serology and histology: In H pylori-positive patients, the mean optical density of the ELISA test was 2.83±0.19, representing a sixfold increase over that of healthy volunteers (0.47±0.27; P<0.001; Figure 6). Cure of infection resulted in a 10% decrease from pretreatment levels (P<0.03; Figure 6).

In patients who failed initial cure, pretreatment mean optical density was 3.59±0.26 (P=0.03 compared with pretreatment cure), and this value remained unchanged following treatment. Moreover, in 80% (four of five) of the patients who failed initial cure, a moderate (n=1) to severe (n=3) pretreatment chronic active gastritis was noted, whereas in cured patients only 30% (six of 20) showed a moderate (n=4) to severe (n=2) pretreatment chronic active gastritis. After treatment, 92% of patients demonstrated either mild chronic gastritis (n=21) or no significant abnormality (n=2), whereas two patients who remained infected still demonstrated severe chronic active gastritis.

Long term acid secretory response: All cured patients dem-
Demonstrated a gradual decrease in BAO and a shift in the pentagastrin dose-response curve to the right (Figure 7). Six months after cure, all patients (n=15) demonstrated a slight decrease in basal and pentagastrin-stimulated acid output. However, the BAO (Figure 1, Table 3), PAO (Figure 3, Table 3) and AUCp (Figure 4, Table 3) failed to reach significance compared with pretreatment levels. Furthermore, the BAO and AUCp remained significantly elevated over pretreatment healthy volunteer levels, whereas the PAO was no longer significantly different.

By one year after cure, in all patients (n=12), the BAO (Figure 1, Table 3), PAO (Figure 3, Table 3) and AUCp (Figure 4, Table 3) returned to pretreatment healthy volunteer levels. The decrease in BAO just failed to reach significance compared with pretreatment levels (P=0.09), whereas the PAO and AUCp decreased significantly (P=0.01 and P=0.05, respectively). No differences were noted between patients treated with sucralfate and those treated with ranitidine.

Serology and histology: In all cured patients, the H pylori IgG concentration continued to decrease over time, with an additional 14% decrease over post-treatment levels at six months, and a further 28% decrease over the six-month level one year after cure (Figure 6). In response to H pylori cure, the histological appearance continued to improve. Six months after cure, of 16 patients in whom an upper gastrointestinal endoscopy with biopsy was performed, seven demonstrated complete resolution of the inflammatory response and nine showed mild nonspecific chronic gastritis. One year after cure, three additional patients showed resolution of the inflammatory response and the remaining three patients had mild nonspecific chronic gastritis.

Parietal cell sensitivity: H pylori-positive patients, irrespective of ulcer healing therapy, failed to demonstrate any differences in either apparent (ED50; Figure 8) or intrinsic (Km;
one month, six months and one year Post Rx. No differences are noted in the K_m in HV Pre Rx and Post Rx and in DU patients Pre Rx, and one month, six months and one year Post Rx.

Figure 9) Intrinsic parietal cell sensitivity (K_m) in healthy volunteers (HV) before treatment (Pre Rx) and after treatment (Post Rx), and in H pylori-positive patients with duodenal ulcer (DU) disease Pre Rx, and one month, six months and one year Post Rx. No differences are noted in the K_m in HV Pre Rx and Post Rx and in DU patients Pre Rx, and one month, six months and one year Post Rx.

Figure 9) parietal cell sensitivity compared with healthy volunteers (Figure 8). In addition, the ED_{50} and K_m remained unchanged in H pylori-positive patients following eradication or in healthy volunteers following sucralfate or ranitidine (Figures 8, 9).

DISCUSSION

In the present study, we investigated the effect of H pylori infection and cure on the gastric acid secretory responses and parietal cell sensitivity in patients with DU disease, and examined the influence of different ulcer treatments on such changes, comparing the study population with healthy volunteers. In addition, we determined the serological and histological responses to H pylori eradication.

One limitation of the present study was the high dropout rate at six months and one year after H pylori eradication due to the difficult nature of the protocol and the good symptomatic response to treatment. There was a 40% patient dropout six months after eradication and a further 12% dropout one year after eradication. However, all attempts were made to maximize follow-up at six months and one year.

All DU patients demonstrated a positive H pylori-specific antibody titre and evidence of chronic active gastritis with H pylori infection. They showed a 2.7-fold greater BAO than healthy volunteers. Eradication of H pylori was accompanied by a 29% reduction in BAO one month after treatment. In contrast, El-Omar et al (13) demonstrated a 50% reduction in BAO. By six months after treatment, a further 10% decrease in BAO was evident, and by one year after treatment, BAO had returned to healthy volunteer levels, in keeping with the findings of Moss et al (30) and El-Omar et al (13).

Similarly, Harris et al (31) demonstrated a decrease in BAO in DU patients after H pylori eradication; however, in that study, BAO levels returned to healthy volunteer levels at six months. Unlike the above studies, the decrease in BAO in our study failed to reach significance. A simple explanation for this is the high degree of variability that was evident between individual patient results confounded by small patient numbers. Similarly, Louw et al (32) demonstrated in a study of nine H pylori-positive DU patients that, after eradication, there was a tendency for basal and low dose pentagastrin-stimulated acid secretion to fall over 12 months following eradication; however, only a reduction in high dose pentagastrin-stimulated acid secretion achieved significance at 12 months. Furthermore, if the BAO values determined from various studies are examined, there is a high degree of variability in the pretreatment BAO (4.1 to 10.7; mean 7.4), suggesting that additional patient/host factors such as cytokine gene polymorphism with cytokine profiles (33,34), blood group antigens, human lymphocyte antigen type, age of infection and environmental exposure (35) are likely important. In addition, the use of different therapeutic regimens may be important. However, despite these potential differences, the BAO was not significantly different among the El-Omar et al (13) study, the Harris et al (31) study and the present study at six months (4.5 and 3 compared with 4.9), or between the El-Omar study and the present study at one year (2.5 compared with 2.9).

Previous studies have indicated that the hypergastrinemia associated with H pylori infection resolves one month after eradication (12,13). This suggests that resolution of additional components of the H pylori-associated inflammatory response is required for the gradual return of BAO to control levels, including morphological changes in parietal cell mass and acid-secretory responses.

In keeping with the results of Isenberg et al (14), the H pylori-positive DU patients demonstrated significantly higher acid secretory responses to each dose of pentagastrin. Moreover, the PAO was increased 1.35-fold compared with healthy volunteer levels, indicating an increase in parietal cell mass in H pylori-positive patients with DU disease. Cure of H pylori infection resulted in complete resolution of the increased acid secretory response and PAO, but with values only returning to healthy volunteer levels by one year after treatment. This gradual decline in the acid secretory response paralleled the decrease observed in BAO.

Previous studies in DU patients have demonstrated an increased parietal cell mass with an increased capacity to secrete acid (7). Because gastrin is a trophic hormone, the long term hypergastrinemia associated with H pylori infection might explain the increased parietal cell mass. In patients with hypergastrinemia secondary to gastrinoma, the increased parietal cell mass generally resolves within three to six months after curative surgery (36). Although gastrin levels were not measured in the present study, we postulate that, with H pylori cure and resolution of the hypergastrinemia (13), there is an associated gradual resolution of the trophic changes in parietal cell mass, with resultant restoration of the acid secretory response to healthy volunteer levels. An additional explanation may lie in the impairment of inhibitory control on gastric secretion at a neuroendocrine level, as suggested by El-Omar et al (13), who showed that H pylori-infected patients with DU had a marked increase in gastrin-releasing peptide (GRP)-stimulated acid output that ap-

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proximated maximal acid secretory capacity. Although GRP stimulates acid secretion via antral G cell-induced gastrin release, which in turn stimulates parietal cells to secrete acid (37,38), GRP also stimulates the release of a variety of other hormones that inhibit acid secretion at both the level of gastrin release and at the parietal cell through the release of somatostatin (39-45). This suggests that the acid response to GRP is the result of a dynamic interaction between these two pathways. In H. pylori-infected individuals, several studies have shown a decrease in stainable D cell concentrations and messenger RNA expression in the gastric mucosa, which suggests, as EL-Omar et al (13) have postulated, that there is an impairment in the GRP-stimulated inhibitory control. Furthermore, the release of soluble mediators associated with the chronic active gastritis likely affects the secretory capacity of parietal cells and contributes to the acid hypersecretion. Thus, with the eradication of H. pylori, the change in cytokine profiles associated with the gradual resolution of the gastritis are likely important contributing factors.

From a clinical perspective Hamlet and Olbe (46) have demonstrated that the increased acid secretion associated with H. pylori results in an increased duodenal acid load. This results in duodenal mucosa injury, the development of gastric metaplasia in the duodenal bulb (47) and subsequent H. pylori colonization of the duodenum. Thus, in addition to gastric acid, H. pylori with associated cytotoxins can induce mucosal damage and lead to the development of DU. One may conclude that, by decreasing gastric acid secretory capacity with eradication of H. pylori from the gastric antrum and duodenal metaplastic epithelium, the duodenitis will diminish and the duodenal mucosa rendered less susceptible to acid attack. Moreover, gastrin levels (AUC gastrin) also fall, and the trophic stimulus to the secretory mass falls with these gastrin levels (AUC gastrin).

Studies comparing parietal cell sensitivity with gastrin levels in patients with DU and healthy volunteers have produced conflicting results. In the present study, despite the observation that H. pylori-infected DU patients secrete more acid than normal healthy volunteers both under basal conditions and in response to graded doses of pentagastrin, no differences were noted in either the apparent or intrinsic parietal cell sensitivity between the two groups or between H. pylori-positive patients before and after treatment. Although these results are in keeping with several studies (29,40,48-50), other studies have suggested an increase in parietal cell sensitivity (14,15). In calculating parietal cell sensitivity from the dose-response curve, it is controversial whether to plot BAO against the zero dose of pentagastrin or to subtract the basal output from the acid output at each pentagastrin dose. This consideration is important when comparing BAO between H. pylori-infected DU patients and healthy volunteers where the values are different. To allow for this potential problem, parietal cell sensitivity was calculated using the method described by Hirschowitz (29) in which apparent sensitivity (D0) is the dose of pentagastrin required to raise the output from basal to 50% of the estimated maximum and K_m is the dose of pentagastrin required to raise the output to 50% of maximum if basal output was zero.

Sucralfate plus triple therapy was associated with a 43% reduction in BAO in H. pylori-infected DU patients, whereas ranitidine triple therapy was associated with only a 7% reduction in BAO. This observation, in conjunction with the findings by Banerjee et al (23), who demonstrated that sucralfate treatment in H. pylori-positive DU patients led to a 50% decrease in BAO, suggests that sucralfate treatment is associated with a reduction in basal acid secretion. Banerjee et al (23) observed a decrease in the density of H. pylori colonization, but not in the severity of the gastritis, suggesting that sucralfate either decreased acid secretion through the suppression of H. pylori infection or that sucralfate decreased the density of H. pylori infection via a direct action. In the present study, we observed an H. pylori eradication rate of 58% with sucralfate-based triple therapy compared with a 92% H. pylori eradication rate with ranitidine-based triple therapy. This observation suggests that, although sucralfate may have a suppressant effect on the H. pylori infection with a resultant reduction in BAO, ranitidine-based triple therapy was more effective in the eradication of H. pylori. These different eradication rates may reflect an enhanced antibacterial action of metronidazole and tetracycline secondary to ranitidine and bismuth, as suggested by Graham et al (51).

In this study, healthy volunteers demonstrated pretreatment BAO and stimulated acid output results that were similar to that seen with both H. pylori-negative and H. pylori-positive healthy volunteers, as shown in the El-Omar study (13). Sucralfate had no effect on the acid secretory response in healthy volunteers, whereas ranitidine was associated with an increase in the acid secretory response as evidenced by a 2.2-fold increase in BAO and a 1.1-fold increase in AUC_p. This observation confirms previous reports (24-26), suggesting that H2-receptor upregulation with acid rebound occurs following ranitidine treatment.

In keeping with the results of Cutler and Prasad (52), eradication of the H. pylori infection was associated with a mean 43% decline in the antibody titre one year after cure. In addition, 75% of the patients examined at one year showed resolution of the gastric inflammation.

In H. pylori-positive DU patients who failed to eradicate the infection, there was a higher pretreatment H. pylori-specific antibody titre with a 1.7-fold increase compared with that of patients achieving primary cure. Moreover, these patients had a higher basal and pentagastrin-stimulated acid secretory response. Following treatment failure, no changes were noted in either the antibody titre or acid secretory response. However, cure of the infection following a second course of treatment with omeprazole and amoxicillin or erythromycin was characterized by a similar decrease in the antibody concentration and acid secretory response to patients achieving initial cure with bismuth-based triple therapy. Although not addressed in the present study, we postulate that the density of H. pylori colonization of the stomach may be important in this regard. Furthermore, ge-
netic and environmental factors may predispose patients to increased bacterial colonization.

Investigators have postulated that the antibacterial activity of amoxicillin may be improved when the pH of gastric juice approaches 7 (53-54). Furthermore, increasing doses of proton pump inhibitors increase the cure rate of H. pylori infection (54). We, therefore, hypothesize that a subgroup of patients with higher serological titres and higher acid secretory response (as observed in those who failed bismuth-based triple therapy) require a greater degree of acid suppression.

In summary, this study has further confirmed that H. pylori-positive DU patients have increased basal and penta- gastrin-stimulated acid secretory responses, which resolve by one year after cure, in conjunction with a decline in serological titres and a resolution of gastric inflammation. However, this study failed to demonstrate that H. pylori-positive DU patients have increased parietal cell sensitivity. In H. pylori-positive DU patients who failed bismuth-based triple therapy, higher serological titres and acid secretory responses were observed, which raises the possibility of greater density of bacterial colonization of the stomach.

Although the mechanisms underlying the increased acid secretory responses in H. pylori-positive patients with DU disease remain unclear, the duration taken for normalization of this response as demonstrated in this study suggests that resolution of parietal cell morphological changes are important.

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REFERENCES


