Ranitidine Versus Colloidal Bismuth Subcitrate in Combination with Amoxicillin and Metronidazole for Eradicating *Helicobacter pylori* in Patients with Duodenal Ulcer

Pedro Carpintero, Margarita Blanco, and José María Pajares

From the Servicio de Medicina Digestiva, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain

One hundred twenty-two patients were randomly assigned to three groups of treatment (A, B, and C), with (1) ranitidine (300 mg q.d. for 6 weeks), (2) ranitidine (300 mg q.d. for 6 weeks) with amoxicillin (500 mg t.i.d.) and metronidazole (500 mg b.i.d.) for the first 12 days, or (3) colloidal bismuth subcitrate (120 mg q.i.d. for 6 weeks) with amoxicillin and metronidazole (at same dosages as in the latter group). Six weeks after the beginning of treatment, an endoscopy showed that ulcers had healed in 49 of 52 patients (94.2%) from whom *Helicobacter pylori* had been eradicated and in 59 of 70 patients (84.3%) from whom it had not (NS). The rates of *H. pylori* eradication in groups A, B, and C were zero, 47.5%, and 86.8%, respectively. At 6, 12, and 18 months, an endoscopy was repeated for monitoring ulcer recurrence and *H. pylori* status. Reinfection rates at 6 months were 42.1% and 15.1% in groups B and C, respectively (*P < .05*). At 18 months, ulcers recurred in 82.9% (63) of 76 patients with noneradicated *H. pylori* infection, vs. 5.7% (2) of 35 patients without *H. pylori* infection (*P < .001*). We conclude that colloidal bismuth subcitrate is more effective for eradication of *H. pylori* than ranitidine when given with amoxicillin plus metronidazole for the treatment of duodenal ulcer, as both early reinfection and ulcer recurrence are diminished.

The problem for patients with duodenal ulcer nowadays is not the healing of the ulcer but the recurrence. Most peptic ulcers heal within 1–2 months of treatment with either H2-receptor antagonists or omeprazole at standard doses. It has been noted that >70%–85% of patients have a recurrence in the first year after finishing conventional treatment for the ulcer and that nine of 10 such patients have symptoms. The maintenance of antisecretory treatment for months or years, depending on the activity of ulcer disease, has been recommended for many patients, but the cumulative rate of recurrence in a year is high [1]. Previous studies [2, 3] showed that the ulcer-healing rate following 2 weeks of bismuth treatment is 35% and after 4 weeks is 84%–90%; only after 8 weeks does it reach 97%–100%.

Eradication of *Helicobacter pylori* modifies the natural history of peptic ulcer disease. In 1994 the National Institutes of Health conference recommended a 2-week bismuth-based triple-drug therapy, which eradicates the infection in 80%–90% of patients infected with *H. pylori* susceptible to metronidazole, as the first-line treatment for patients with peptic ulcer [4]. This regimen is complex, leading to poor compliance, which, together with antimicrobial resistance to nitroimidazoles (a major factor), is the usual cause of treatment failure [5]. Published data show a clear benefit in terms of a decrease in the duodenal and gastric ulcer recurrence rate when *H. pylori* is eradicated. Eradication can reduce the recurrence rate from 80% to 20% at the 1-year follow-up [6–9], and this reduction extends to at least 7 years after treatment [10]. The primary objective of our study was to compare the efficacy of ranitidine vs. colloidal bismuth subcitrate in combined treatment with amoxicillin and metronidazole in the eradication of *H. pylori* from patients with duodenal ulcer. A secondary objective was to ascertain the rate of recurrence of duodenal ulcer related to *H. pylori* infection during a follow-up of 18 months.

Materials and Methods

Patients

We selected 122 patients from a group of 307 included in a concurrent ecological study, which evaluated the prevalence of *H. pylori* infection, its topographic distribution in the stomach, and histologic lesions of the gastric mucosa. These 307 patients, with active duodenal ulcers larger than 5 mm in diameter, had been referred to our department for an oral panendos-
copy (Olympus JF 1T20, Medical Europe, Barcelona) and presented with upper digestive tract symptoms. Criteria for exclusion from the study were recent digestive bleeding, coagulation disorders, intake of antulcer treatment (except antacids) in the preceding month, previous abdominal surgery, or malignant lesions. Patients treated with antibiotics or nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids before the endoscopy were not excluded from the ecological study. In each case, it was noted whether the patient had a daily smoking habit.

Of all the patients with duodenal ulcers, 122 were enrolled in the trial. Conditions for inclusion in the study were as follows: active duodenal ulcer and *H. pylori* infection; age of 18–65 years; a signed informed consent form; acceptance of the conditions of the study and the prescribed revisions; no long-term use of drugs (such as NSAIDs or corticosteroids) due to other diseases; no antibiotic use in the preceding 4 weeks; no contraindication for endoscopy and/or biopsy; no previous allergy to penicillin and derivatives; and no participation in other therapeutic trials.

**Study Design**

A randomized and controlled clinical trial was designed to evaluate the efficacy of two different regimens in the eradication of *H. pylori* in cases of duodenal ulcer. One hundred and twenty-two patients with duodenal ulcer and *H. pylori* infection were randomly assigned to three treatment groups that were homogenous in age, sex, and smoking habits. Each included ∼40 individuals to optimize the statistical analysis. The treatment assignments were determined by a list of random numbers generated by computer. Patients were monitored for 18 months for ulcer recurrence and status of *H. pylori* infection.

Group A (44 patients) received ranitidine (Zantac; Glaxo, Madrid) at a dosage of 300 mg q.d., given 1 hour after dinner for 6 weeks. This group was considered to be the control group, as the other two received treatment with the intention to eradicate *H. pylori* infection. Group B (40 patients) received ranitidine (300 mg q.d., also given 1 hour after dinner for 6 weeks) plus amoxicillin (Clamoxy; SmithKline Beecham, Madrid) at a dosage of 500 mg t.i.d. and metronidazole (Flagyl; Rhone-Poulenc Rorer, Madrid) at a dosage of 500 mg b.i.d.; the latter two were given before meals for the first 12 days. Group C (38 patients) received colloidal bismuth subcitrate (Gastrodenol; Cantabria Laboratories, Santander, Spain) at a dosage of 120 mg q.i.d., given before meals for 6 weeks, plus amoxicillin and metronidazole, administered as in group B. A 12-day duration of antibiotic treatment was considered most practical because of the packaging of the drugs in Spain.

In the 6th week a second endoscopy was done to confirm healing. If the duodenal ulcer was not healed, treatment (with ranitidine or colloidal bismuth subcitrate) was maintained for 2 more weeks and a third endoscopy was performed afterward. After the clinical trial, and following endoscopic confirmation of duodenal ulcer healing, all three groups of patients were included in an 18-month prospective longitudinal cohort study of the natural evolution of the disease and of the rate of ulcer recurrence in relation to *H. pylori* infection. At 6, 12, and 18 months after the initial diagnosis, an endoscopy was performed to observe the gastroduodenal mucosa and to obtain biopsy specimens for histologic examination and culture for *H. pylori*. Reversion to a positive *H. pylori* status indicated reinfection.

**Definition of Endpoints**

Eradication was defined as absence of the organism at reevaluation 4 weeks after the end of antibiotic treatment. Eradication was the clinically important endpoint of the trial. Clinical adverse effects were recorded and evaluated for severity, outcome, and relationship to the drugs used. Definition of ulcer recurrence required an endoscopic reevaluation, which was proposed to patients who presented with digestive symptoms lasting >1 week. If recurrence of the ulcer was confirmed, retreatment was proposed.

**Clinical and Laboratory Assessment**

Status of *H. pylori* infection was defined by histologic and microbiological methods. A patient was considered infected when culture-positive for *H. pylori* or if two of the following histologic methods yielded positive results: urease test (Clo-test [Delta-West, Western Australia], Cutest [Temmler Pharma, Marburg, Germany], Cristensen solution), direct histologic examination (hematoxylin/eosin, Giemsa, and Warthin-Starry silver staining), and examination with gram or acridine orange stains. Biopsy specimens were taken from the antrum (1 for culture, 1 for a urease test, and 2 for histologic examination). Both histlogic and microbiological studies were done without knowledge of either the identity of the patient or the treatment received.

Lesions of gastric mucosa were graded according to the methods of Kekki et al. [11] for the classification of gastritis. The culture medium used was agar supplemented with 5% lysed horse blood and selective Skirrow supplement, and cultures were incubated for 5–7 days in microaerophilic conditions. The bacterium was identified by gram staining and biochemical activity tests for urease, catalase, and oxidase.

**Statistical Analysis**

Continuous data, presented as mean ± SE, were compared by Student’s *t*-test. Proportional data were compared by *χ*², with Yates’ correction and Fisher’s exact test used when necessary. All tests performed were two-tailed. A *P* value of <.05 was considered significant. Statistical calculations were performed with the statistical software package RMSigma 2.0 (Horus Hardware).
Results

One hundred and twenty-two patients with duodenal ulcer and *H. pylori* infection participated in the study. The characteristics of patients were similar in the three groups (table 1). The mean age was 46 ± 9.2 years, and there were 79 males (64%) and 43 females (46%). Most of the patients (92; 75.4%) were smokers; most smokers were male (91.1%, vs. 46.5% female).

The average incidence of side effects was 11.5% (14 of 122). A case of dizziness occurred in group A (2.3%; 1 of 44) in association with ranitidine. Six group B patients (15%; 6 of 40) had side effects: diarrhea (3), abdominal and epigastric pain with nausea (2), and skin rash that disappeared at the end of the treatment with antibiotics (1). Seven patients in group C (18.4%; 7 of 38) had side effects: epigastric disturbances, nausea, and cephalgia (3); moderate diarrhea (2); intense constipation with abdominal pain and mouth dryness (1); and glossitis and candidal vulvovaginitis (1). No statistical difference in side effects was found between the groups taking antibiotics (P = .68). None of the patients’ symptoms were severe enough to necessitate withdrawal from the study.

Ulcer Healing

In the 6th week after the beginning of treatment, healing of ulcers was confirmed in 80.3% of the patients (108 of 122). Treatment with ranitidine or colloidal bismuth subcitrate was prolonged for 2 more weeks for the 14 patients not healed, and in the 8th week another endoscopy was performed. This confirmed the healing of ulcers in 117 patients (95.9%) (6 vs. 8 weeks, NS; P = .055). The five unhealed patients continued treatment for 2 more weeks, and healing was checked again in the 10th week.

The rates of duodenal ulcer healing in the different treatment groups at weeks 6 and 8 are shown in table 1. The rates were similar in all three groups at 6 weeks (86%, 90%, and 89%) and at 8 weeks (93%, 95%, and 97%), with no statistically significant differences (χ², 2 df: P > .05).

In the 6th week duodenal ulcer healing was achieved in 49 of 52 patients (94.2%) from whom *H. pylori* had been eradicated and in 59 of 70 patients (84.3%) in whose gastric mucosa *H. pylori* persisted (χ² with Yates correction: P = .15).

Follow-Up

During follow-up 11 patients were excluded who did not present for the prescribed endoscopy; spontaneously took anti-ulcer treatment because of digestive symptoms; had acute myocardial infarction; moved to another city; had recurrence of ulcers with digestive bleeding; underwent urgent gynecologic surgery that required antibiotic therapy for a long period; or became pregnant. These withdrawals are summarized as follows: group A, 2 patients after the 9th month and 3 patients after the 15th; group B, 1 patient after the 9th month and 1 after the 15th; and group C, 1 patient after the 3rd month, 1 after the 9th, and 2 after the 15th.

Eradication of *H. pylori*

There were no cases of eradication of *H. pylori* in the control group (group A). *H. pylori* status and reinfection rates during follow-up are shown in tables 2 and 3, respectively. In group B, treatment with ranitidine and the two antibiotics eradicated *H. pylori* infection in 19 of 40 patients (47.5%). In group C, colloidal bismuth subcitrate achieved eradication in 33 of 38 patients (86.8%). At 18 months of follow-up, the eradication rate was 23.6% (9 of 38 patients) in group B and 76.4% (26 of 34 patients) in group C. Both differences in eradication were statistically significant (P < .001). Reinfection rates at 6 months were 42.1% (8 of 19) and 15.1% (5 of 33) in groups

| Table 1. Characteristics of patients in treatment groups A, B, and C and the duodenal ulcer healing rates with the three regimens at 6 and 8 weeks after treatment began. |
|-------------------------------|---|---|---|---|
| Variable                      | A | B | C | Total |
| No. of patients               | 44 | 40 | 38 | 122 |
| Male/female                   | 28/16 | 27/13 | 24/14 | 79/43 |
| Age (y) Mean ± SD             | 44.1 ± 10 | 45.6 ± 9.2 | 43.3 ± 10.4 | 46 ± 9.2 |
| Range                         | 19–63 | 18–65 | 20–61 | 18–65 |
| No. of smokers (male, female) | 33 (26, 7) | 29 (24, 5) | 30 (22, 8) | 92 (72, 20) |
| Percentage (no.) of patients with Side effects | 2.3 (1) | 15 (6) | 18.4 (7) | 11.5 (14) |
| DU healing at 6 w             | 86 (38) | 90 (36) | 89 (34) | 80.3 (108) |
| DU healing at 8 w             | 93 (41) | 95 (38) | 97 (37) | 95.9 (117) |

NOTE. See Materials and Methods section for treatment group regimens. DU = duodenal ulcer.
Table 2. Effect of treatment on eradication of Helicobacter pylori at 6 weeks and 6, 12, and 18 months after treatment began.

<table>
<thead>
<tr>
<th>Treatment group (n)</th>
<th>No. (%) of H. pylori–negative patients at indicated time</th>
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<tbody>
<tr>
<td></td>
<td>6 w</td>
</tr>
<tr>
<td>A (44)</td>
<td>0/44</td>
</tr>
<tr>
<td>B (40)</td>
<td>19/40 (47.5)</td>
</tr>
<tr>
<td>C (38)</td>
<td>33/38 (86.8)</td>
</tr>
</tbody>
</table>

NOTE. See Materials and Methods section for treatment group regimens. All P values were <.001 in comparisons between groups B and C.

Table 4. Number and accumulated percentage of duodenal ulcer recurrences (R) in the three treatment groups during follow-up.

<table>
<thead>
<tr>
<th>Follow-up month</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>44</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>7</td>
<td>7</td>
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<tr>
<td>18</td>
<td>39</td>
<td>16</td>
<td>34</td>
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</table>

NOTE. See Materials and Methods section for treatment group regimens. In comparisons among the three groups, \( \chi^2 = 6.9 \) \((P < .05, 2 \text{ df})\) at 6 mo, \( \chi^2 = 21.5 \) \((P < .001, 2 \text{ df})\) at 12 mo, and \( \chi^2 = 33.6 \) \((P < .001, 2 \text{ df})\) at 18 mo.

Ulcer Recurrence

Patients were monitored for recurrence of ulcers. The number of recurrences was counted monthly and cumulatively. Corresponding percentages were calculated with respect to the number of patients remaining in the study each month. Results are shown in table 4. The groups were compared at 6, 12, and 18 months. Group A had the greatest rate of duodenal ulcer recurrence: 36.4%, 71%, and 87.2%, respectively, at 6, 12, and 18 months. In group B the respective rates were 17.5%, 41%, and 63.2%. The best results were achieved in group C, with duodenal ulcer recurrence rates of 13.5%, 19.4%, and 20.6%, respectively. The differences among the three groups were statistically significant: \( \chi^2 = 6.9 \) \((P < .05, 2 \text{ df})\) at 6 months, \( \chi^2 = 21.5 \) \((P < .001, 2 \text{ df})\) at 12 months, and \( \chi^2 = 33.6 \) \((P < .001, 2 \text{ df})\) at 18 months.

To reduce bias, we also analyzed the results with data from the 11 patients lost during follow-up by counting patients in groups A and B as having no recurrences during follow-up and the patients lost in group C as all having recurrences. We thus obtained a significant value of \( \chi^2 = 19.6 \) \((P < .001, 2 \text{ df})\) and rates of ulcer recurrence of 77.3% in group A, 60% in group B, and 28.9% in group C at 18 months of follow-up.

The evolution of ulcer recurrence was analyzed to ascertain the influence of H. pylori infection and its possible implication in the more frequent rate of ulcer recurrence in groups A and B than in group C. We compared the number of patients in each group and their H. pylori status at the time of the recurrence. At the end of 18 months of follow-up, the recurrence rate was 82.9% (63 of 76) among patients in whom H. pylori infection persisted, vs. 5.7% (2 of 35) among patients without H. pylori infection \((P < .001)\). The relative risk of recurrence of duodenal ulcer was 14.5 times greater \((\text{RR} = 14.5; 95\% \text{ CI}, 3.76–55.94)\) in patients still infected with H. pylori than in patients from whom it was eradicated. In duodenal ulcer recurrences, the risk attributable to H. pylori infection in cases of noneradication is 77% \((95\% \text{ CI}, 0.71–0.83)\). This figure may be considered the proportion by which ulcer recurrence would be reduced if H. pylori infection were eradicated.

Discussion

Eradication of H. pylori modifies the natural history of peptic ulcer disease. Triple-drug therapy with bismuth plus metronidazole and amoxicillin achieved eradication in 73.1%, with no significant number of withdrawals despite a greater number of side effects \([12, 13]\). The highest eradication rates (up to 94%) have been achieved with triple-drug therapy that includes metronidazole, tetracycline, and bismuth salts given for 4 weeks. In the search for the ideal anti-H. pylori treatment regimen, combinations of amoxicillin and metronidazole with either omeprazole or ranitidine have also been studied.

A 2-week regimen of omeprazole, amoxicillin, and metronidazole achieved eradication in 96.4% of 55 patients infected with metronidazole-susceptible H. pylori and in 75% of 72 patients infected with metronidazole-resistant organisms \([14]\). Hentschel et al. achieved similar results using ranitidine, amoxicillin, and metronidazole \([15]\). In our study, therapy with ranitidine plus amoxicillin and metronidazole eradicated H. pylori infection in 47.5% of duodenal ulcer cases, and colloidal bismuth subcitrate with the same antibiotics achieved eradication in 86.8%.

The success rate of any H. pylori eradication regimen containing metronidazole is critically dependent on the frequency of metronidazole susceptibility of isolates from the population.
treated. Chiba et al. [16] pointed out that nitroimidazole susceptibility may help to explain the wide range of eradication rates (31.6%–78.9%) found in the trials using bismuth plus metronidazole. It has been speculated that the presence of metronidazole-resistant strains would lead to very different rates of reinfection/late recrudescence in different populations [17]. In our hospital area, 8.9% of strains have been metronidazole-resistant [18]. We did not evaluate resistance in our patients, but it is possible that zero to 30% of therapy failures in groups B and C were due to metronidazole resistance.

Side effects occur in approximately one-third of patients taking triple-drug therapy, and 4%–17% of patients discontinue therapy because of side effects. Side effects described in previous studies include nausea/vomiting, diarrhea, rash, and pseudomembranous colitis [9]. In our trial, side effects of triple-drug therapy were moderate and occurred at a rate similar to that in other studies (18.4%), but none of the patients with side effects withdrew from therapy.

Eradication of H. pylori can accelerate healing of duodenal peptic ulcer [15, 19–21]. Five of the patients in our study needed therapy for 10 weeks to heal the ulcers, which were considered refractory. Smoking and persistence of H. pylori can play a role when ulcers heal slowly [22, 23]. In the 6th week, duodenal ulcer healing was achieved in 94.2% of patients from whom H. pylori had been eradicated, vs. 84.3% of patients in whom it persisted. The difference is not significant probably because of the small samples.

Reduced ulcer recurrence rates have been reported with use of regimens of antibiotics or bismuth salts that do not modify acid secretion but can eradicate H. pylori [8, 9]. In our study, the rates of ulcer recurrence at 18 months in group A (ranitidine) and group B (ranitidine plus amoxicillin and metronidazole) were 87.2% and 63.2%, respectively (P < .05). The difference between the groups (24%) is explained only by the action of the antibiotics on H. pylori, since the percentages of eradication in groups A and B were zero and 26.3%, respectively. In group C (colloidal bismuth subcitrate plus amoxicillin and metronidazole) the most important reduction of ulcer recurrence was achieved, as only seven of 34 patients (20.6%) had a recurrence in 18 months. The rate of H. pylori eradication was best in this group (76.4%).

When we considered data from the patients who withdrew as good results, we still obtained significant figures. The differences between results in group B and C were probably due to the use of bismuth salts, which have a double effect, in that they are protective to the mucosa and bactericidal to H. pylori, although the latter property seems to be the principal one [10, 24, 25].

Our results at the end of the 18 months of follow-up show that patients in whom H. pylori infection was not eradicated had 82.9% of ulcer recurrences, vs. the 5.7% in patients without H. pylori infection (P < .001). The relative risk of duodenal ulcer recurrence is 14.5 times greater in patients infected with H. pylori than in those from whom it is eradicated. Thus, in duodenal ulcer recurrences, the risk attributable to H. pylori infection in cases of noneradication was 77%; ulcer recurrences would be reduced by this amount if H. pylori infection were eradicated.

No adequate follow-up data exist on true reinfection rates following H. pylori eradication in patients with previous duodenal ulcer disease. It should be observed that if reinfection is a frequent phenomenon, then little advantage would be gained by use of short-term antibiotic therapy instead of long-term therapy with H2-receptor antagonists. Using four routine techniques for diagnosis, Xia et al. [26] reported a recrudescence rate of 14.3% in patients treated with triple-drug therapy including amoxicillin and of 47.1% in patients treated with colloidal bismuth subcitrate alone; this raises questions regarding the adequate duration of testing for H. pylori eradication.

A study of 190 patients [27] after eradication of H. pylori found that the risk of ulcer recurrence was 1% during each of the first 2 years of follow-up and zero during the 3rd and 4th years. Many investigators that have not segregated the first year from subsequent years of follow-up report unusually high reinfection rates in the first 12 months, with dramatically reduced reinfection subsequently [28, 29]. We found reinfection rates at 6 months of 42.1% and 15.1%, respectively, with ranitidine and colloidal bismuth subcitrate. This significant difference was not confirmed in the second or third semesters of follow-up, so early reinfection or late recrudescence exists.

It has been pointed out that many trials using colloidal bismuth subcitrate have high recrudescence rates. The hypothesis would be that colloidal bismuth subcitrate may have unusual bacteriologic effects, resulting in slow repopulation of the stomach by H. pylori after cessation of therapy [26]. The multiple antral and corporal biopsy specimens used in our study should have ensured high sensitivity, so the sample error should be small. Staining with Giemsa and Warthin-Starry silver stains probably enhances the ability to detect H. pylori in the gastric mucosa.

Our conclusions are as follows. (1) The eradication rate with the regimen of ranitidine plus amoxicillin and metronidazole was 47.5%, and that with the regimen of colloidal bismuth subcitrate plus amoxicillin and metronidazole was 86.8% (P < .001). (2) The reinfection rate at 6 months was higher with use of ranitidine than with colloidal bismuth subcitrate, although there was no difference in later reinfection rates between the two. (3) No significant differences were found in duodenal ulcer healing rates at 6 weeks among patients from whom H. pylori was or was not eradicated. (4) The duodenal ulcer recurrence rate is significantly lower with use of colloidal bismuth subcitrate than with ranitidine when given with amoxicillin and metronidazole, because the regimen better eradicates H. pylori.

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References