Omeprazole-based Dual and Triple Regimens for *Helicobacter pylori* Eradication in Children

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ABSTRACT. *Objective.* **To evaluate the efficacy and safety of omeprazole-based dual and triple regimens for the treatment of children with *Helicobacter pylori* infection.**

Methods. **Twenty-two patients (3 with gastric ulcer, 12 with duodenal ulcer, and 7 with nodular gastritis alone) were studied. Twelve ulcer patients also had nodular gastritis. The dual regimen included a 2-week course of omeprazole (0.6 mg/kg twice a day) and amoxicillin (30 mg/kg twice a day) (n = 10), and the triple regimen included the dual regimen plus clarithromycin (15 mg/kg twice a day) (n = 12). In patients with active ulcers, omeprazole once daily was administered for another 4 weeks. Endoscopic biopsies were taken before therapy and 4 weeks after completion of a 2-week course of therapy, and patients were followed for 6 months. The gastritis score (grade 0 to 3) and serum anti-*H pylori* IgG antibody titers were also determined.**

Results. **The regimens were tolerated by all patients. Eradication rates for the dual and triple regimens were 70% and 92%, respectively. Active ulcers completely healed within 6 weeks. Patients with nodular gastritis alone showed different clinical responses to therapy. Pretreatment histology showed chronic gastritis in all patients. Successful *H pylori* eradication significantly reduced the mean gastritis score from 2.9 to 1.3, but unsuccessful eradication did not reduce it. The disappearance of antral nodularity often coincided with the success of eradication. Successful eradication significantly decreased pretreatment serum anti-*H pylori* IgG antibody titers by 29% at 1 month, by 52% at 3 months, and by 67% at 6 months. Side effects were mild and were reported in 23% of patients.**

Conclusion. **An omeprazole-based regimen is safe and may be a better option for eradication of *H pylori* in children. Antral nodularity is a macroscopic marker of *H pylori* infection. *Pediatrics* 1997;100(1). URL: http://www.pediatrics.org/cgi/content/full/100/1/e3; *Helicobacter pylori, gastritis, omeprazole, amoxicillin, clarithromycin.***

Helicobacter pylori infection is a major etiological factor in chronic gastritis and is highly associated with peptic ulcer disease.[1,2] Eradication of *H pylori* dramatically reduces the recurrence rate of duodenal ulcer.[3,4] Therefore, the aim of treatment for *H pylori*-associated peptic ulcer disease has changed from the mere suppression of gastric acidity to eradication of the organism. The National Institutes of Health recommended treatment with antimicrobial agents in addition to antisecretory drugs, regardless of whether recurrence occurs.[5] In adults, high eradication rates (90% or higher) have been obtained with a traditional bismuth-based triple regimen that includes metronidazole and either amoxicillin or tetracycline.[6,7] However, this regimen has disadvantages (such as complex administration and side effects) which lead to poor patient compliance in clinical practice. Metronidazole-resistant strains are also a problem. Recently, as an alternative to the traditional triple regimen, a simple omeprazole-based regimen has been introduced with a low incidence of side effects.[8,9] This regimen has been most widely studied.[10,11]

H pylori eradication with bismuth-based regimens has been also attempted in children with peptic ulcer disease or gastritis.[12–18] However, there are few studies of omeprazole-based regimens.[19] This study reports on the efficacy and safety of omeprazole-based dual and triple regimens in children with *H pylori*-associated gastroduodenal diseases.

PATIENTS AND METHODS

Patients

Between March 1995 and February 1996, 22 patients (age 8 to 16 years) were enrolled in this study (Table 1). Three patients had gastric ulcers, 12 had duodenal ulcers, and 7 had nodular gastritis with symptoms including epigastric pain, nausea, or vomiting. Nodular gastritis was also found in 12 of 15 patients with peptic ulcer disease. Among 10 patients with active ulcers, 2 received eradication therapy at the first presentation of the disease and 8 at recurrence. The clinical symptoms of these patients included hematemesis, epigastric pain, tarry stool, and/or anemia. At presentation, one patient with bleeding gastric ulcer and one with bleeding duodenal ulcer underwent endoscopic hemostasis with pure ethanol using a method reported previously.[20] Five asymptomatic patients with a history of ulcer recurrence received eradication therapy for prevention of recurrence; the patients and their parents requested the therapy. None of the patients received either steroids or nonsteroidal antiinflammatory drugs. There was one smoker who was male and 16 years old.

Informed consent was obtained from all patients and their parents before inclusion.

Treatment and Follow-up

Patients undergoing maintenance treatment with H2-receptor antagonists stopped the drugs at entry. In patients with active ulcers, eradication therapy was started after *H pylori* infection was confirmed by the rapid urease test (Stat-Urease, PML Microbiologicals, Canada). Drug dosage within each eradication regimen was based on the adult experience with high-dose regimens, including 20 mg omeprazole twice a day.[10,11] The first 10 patients received the dual regimen: 0.6 mg/kg (maximum dose, 20 mg) omeprazole twice a day and 30 mg/kg (maximum dose, 1000 mg) amoxicillin twice a day at breakfast and at the evening meal for 14 days. The other 12 patients received the triple regimen: the dual

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regimen plus 15 mg/kg (maximum dose, 500 mg) clarithromycin twice a day for 14 days. In patients with active ulcers, once-daily omeprazole (0.6 mg/kg with a maximum dose of 20 mg) was administered for another 4 weeks. Patients without active ulcers or with nodular gastritis alone received only a 2-week course of eradication therapy.

Upper gastrointestinal endoscopy and biopsy were routinely performed before therapy and 4 weeks after completion of a 2-week course of treatment (at 6 weeks). Each patient was followed up for at least 6 months.

H pylori Infection and Gastritis

Two biopsy specimens were taken from the gastric antrum. The specimens were stained with hematoxylin-eosin and Giemsa for the histological investigation which included an *H pylori* test. Another two antral biopsies were examined for culture and urease activity of *H pylori*. The *H pylori* test was considered positive if at least one test (histology, culture or urease) gave a positive result. If all results were negative at 6 weeks, *H pylori* was considered to be eradicated. The antral biopsy specimens before and after eradication therapy were also studied for the degree of gastritis (Table 2). The degree of inflammation was graded according to Bazzoli et al:[21] grade 0, normal gastric histology; grade 1, slight increase in the number of mononuclear cells; grade 2, increase in the number of mononuclear cells and neutrophils also present; grade 3, increase in the number of mononuclear cells and neutrophils with epithelial invasion of neutrophils. The pathologist (H.N.) was unaware of the clinical course of the patients.

Serum IgG antibody against *H pylori* was measured using an enzyme immunoassay (Cobas Core Anti-*H pylori*-EIA, Nippon Roche, Japan) with a cutoff point of 6 U/mL. Blood samples were obtained before treatment and at 1, 3, and 6 months after treatment ended; they were frozen at −20°C. To avoid day-to-day and tube-to-tube variations, investigators collectively measured the samples with the same lots of the assay kit.

TABLE 1. Demographic Characteristics of Patients

	Dual Regimen	Triple Regimen	*P*
Patients	10	12	
Mean age (y) (range)	12.4 (8–16)	13.2 (10–16)	NS*
Sex (M/F)	7/3	5/7	NS
Gastric ulcer	2	1	
Duodenal ulcer	6	6	
Nodular gastritis	2	5	
Eradication rates (%)	70	92	NS
Side effects (%)	10	33	NS

* NS, not significant.

Intragastric pH Monitoring

To evaluate acid suppression with omeprazole in six patients, intragastric acidity was monitored for 24 hours (model KR-5010 pH monitor, Kuraray Co., Ltd., Japan) on days 5 to 13 of eradication therapy. After calibration, the electrode was transnasally positioned in the middle body of the stomach under fluoroscopy. The data were transferred to a personal computer and analyzed with respect to mean intragastric pH and H^+ activity.[22]

Safety Assessment

Drug tolerance was investigated by questioning patients and parents about possible side effects: altered taste, diarrhea, nausea/vomiting, abdominal pain, skin eruption, and neurological symptoms (such as headache and dizziness). Laboratory examinations (including hemoglobin levels, white blood cell counts, platelet counts, serum electrolyte levels, hepatic and renal function tests, and urinalysis) were performed during therapy and at follow-up. Serum gastrin levels were also measured in all patients.

Statistics

The differences in age and sex ratio of patients, frequency of side effects, and eradication rates between dual and triple regimens were analyzed by Fisher's exact test, and differences in the mean gastritis score and serum anti-*H pylori* IgG antibody titers before and after eradication therapy were analyzed by the paired *t* test. A value of $P < .05$ was considered significant. The values were presented as mean ± SEM.

RESULTS

Eradication and Gastritis

The first endoscopy demonstrated antral nodularity in 19 patients, multiple erosions in 2, and no macroscopic lesions in 1 (Table 2). Pretreatment histology showed chronic gastritis in all patients (mean gastritis score, 2.9). In 14 patients (13 with the nodu-

TABLE 2. Antral Nodularity and Gastritis Score With Eradication Therapy

Patient No.	Age (y)/Sex	*H pylori**		Antral Nodularity**		Gastritis Score	
		Before	After	Before	After	Before	After
1	11/F	+	−	++	−	3	1
2	16/M	+	−	++	−	3	2
3	8/F	+	−	+	−	3	1
4	13/F	+	−	+	−	3	2
5	10/M	+	−	+	−	3	2
6	16/M	+	−	+	−	2	2
7	14/F	+	−	++	±	3	1
8	14/M	+	−	++	±	3	1
9	13/F	+	−	+	±	3	1
10	13/M	+	−	+	±	2	2
11	14/M	+	−	++	+	3	1
12	14/F	+	−	++	+	3	2
13	14/F	+	−	++	+	3	2
14	13/M	+	−	+	+	3	2
15	16/M	+	−	+	+	3	3
16	15/M	+	−	−§	−	3	1
17	8/F	+	−	−‖	−	3	1
18	12/M	+	−	−§	−	3	2
19	13/M	+	+	++	+	3	3
20	11/F	+	+	+	+	2	2
21	14/M	+	+	+	±	3	2
22	10/F	+	+	+	±	3	2

* +, Positive; −, negative.
** ++, Moderate to severe; +, mild; ±, slight; −, not found.
§ Erosions.
‖ Endoscopically normal.

larity and 1 with erosions but no nodularity), pretreatment histology demonstrated lymphoid follicles predominantly in the lamina propria. No patient had intestinal metaplasia.

Examinations of the second biopsy specimens demonstrated that *H pylori* was eradicated in 7 of 10 patients (70%) with the dual regimen and 11 of 12 patients (92%) with the triple regimen (Tables 1 and 2). There was no difference in eradication rate between regimens ($P = .19$). In all 10 patients with active ulcers, the symptoms ceased within several days after the initiation of therapy and the ulcers completely healed with a full 6-week course of treatment. Antral nodularity disappeared in 6 of 15 patients with successful eradication (Table 2). Successful eradication therapy significantly reduced the mean gastritis score from 2.9 to 1.6 ($P < .005$), but unsuccessful eradication did not reduce it ($P = .50$). Lymphoid follicles were detected in 11 patients after eradication therapy.

Intragastric Acidity

With the eradication therapy, the mean intragastric pH was 4.7 ± 0.3 (range, 3.5 to 6.0) and the mean intragastric H^+ activity was 0.99 ± 0.29 mmol/L (range, 0.04 to 2.06). The percentages of time at a pH of 2 or more, at a pH of 3 or more, and at a pH of 4 or more were 96.9 ± 1.2%, 85.3 ± 3.8%, and 64.7 ± 8.3%, respectively.

Serum Anti-*H pylori* Antibody

Two patients were excluded from this serological study, because they were seronegative at entry. Of the remaining 20 patients, the mean pretreatment titer of anti-*H pylori* IgG antibody was 66.9 U/mL (range, 7.8 to 567.9). In successfully treated patients, the IgG antibody titer decreased by an average of 29% at 1 month ($P < .001$), by 52% at 3 months ($P < .001$), and by 67% at 6 months ($P < .001$), compared with the pretreatment titers (Fig 1). Two patients became seronegative at 6 months. In contrast, the IgG antibody titers remained at baseline levels in patients with persistent *H pylori* infection. Two patients who were excluded from this serological study continued to be seronegative in the follow-up period.

Safety and Follow-up

Drug compliance was good in all patients. The overall incidence of side effects was 23%; diarrhea was recorded in one patient given the dual regimen, and metallic taste, dry mouth, and/or diarrhea in four patients given the triple regimen (Table 1). Because the side effects were mild, however, discontinuation of treatment was not necessary. Laboratory examinations showed no abnormalities during or after therapy. Although serum gastrin levels were greater than normal at 2 to 4 weeks after treatment started, they normalized within 3 months.

In patients with nodular gastritis alone in whom *H pylori* was eradicated, the symptoms disappeared in two patients, improved in three, and persisted in two at 6 months. One patient with unsuccessful therapy continued to have epigastric pain. Some patients took 3 to 6 months to confirm a symptomatic response to eradication therapy. Ulcer recurred 3 months after treatment ended in one patient with duodenal ulcer in whom *H pylori* was not eradicated. In the remaining ulcer patients, however, ulcer did not recur in the follow-up period (ranging between 6 and 17 months). In four patients with successful eradication who agreed to endoscopic biopsy at 6 months, *H pylori* colonization continued to be negative.

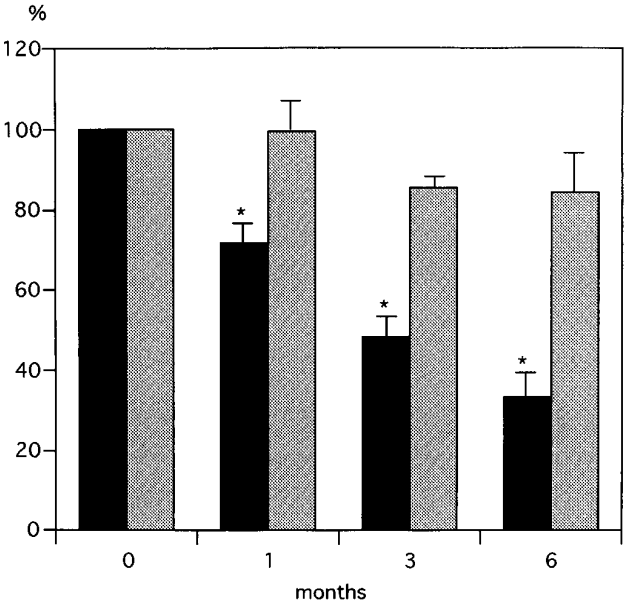

Fig 1. Serum anti-*H pylori* IgG antibody titers. Posttreatment titers are expressed as percentages of pretreatment levels in successfully treated (solid bars) and unsuccessfully treated (shaded bars) patients. *$P < .001$.

DISCUSSION

An omeprazole-based regimen consists of the combination of omeprazole with one or two antibiotics effective against *H pylori.* Amoxicillin has a low minimum inhibitory concentration for *H pylori* in vitro, but its monotherapy demonstrates low eradication rates of 20%.[6] Because amoxicillin operates optimally at neutral pH levels, decreasing intragastric acidity with omeprazole seems to be important in eradicating *H pylori.* Omeprazole is an essential component of new eradication regimens.[10] However, eradication rates with a dual regimen of omeprazole/amoxicillin vary from study to study, with a pooled rate of 60%.[23] It has been speculated that differences in *H pylori* strains or host factors may explain the discrepancies among studies.[24] The role of omeprazole in an amoxicillin dual regimen also holds true for that in a clarithromycin dual regimen. On the dual regimen, clarithromycin is almost equal to amoxicillin with respect to the eradication rate and safety.[10] Katelaris et al stated that amoxicillin is the first choice for omeprazole dual regimens, however, because clarithromycin-resistant strains are demonstrated in 5 to 10% of patients.[25]

Many adult studies using 20 to 40 mg/day omeprazole have been attempted. In one pediatric study with 20 mg omeprazole daily and 250 mg or 500 mg amoxicillin twice a day, *H pylori* was eradicated in

only two of eight patients.[19] We previously reported that an average of 0.6 mg/kg daily of omeprazole is appropriate in most children with H2-receptor antagonist-resistant acid-related diseases.[22] The dose of omeprazole in this study is twice as high as the suggested dose, which is relatively high for children compared with 40 mg daily in adults. The pH study has shown that 1.2 mg/kg daily of omeprazole powerfully reduces intragastric acidity, although the reduction may be insufficient in some patients. Eradication rates do not differ between 20 mg and 40 mg twice daily of omeprazole.[26] A dose more than 1.2 mg/kg daily of omeprazole might be unnecessary in children.

The current belief is that an eradication rate more than 90% is essential for an ideal regimen. Additionally, simplicity of drug administration, low doses of antibiotics and a low incidence of side effects are desirable.[10] On these grounds, wide study of omeprazole-based triple regimens shows that eradication rates of around 90% have been achieved;[10,11] the two antibiotics prescribed are usually amoxicillin and clarithromycin or a nitroimidazole. However, there are only a few reports describing a regimen consisting of omeprazole, amoxicillin, and clarithromycin.[27,28] The advantage of this regimen is that the risk of nitroimidazole resistance is excluded. This study showed a high eradication rate, which is consistent with the results of adult studies.[10,11,27,28] Although there was no statistical difference between dual and triple regimens (this study was not randomized), it may be attributable to the small number of patients studied. We believe that an omeprazole-based regimen is safe and a better therapeutic option for children with *H pylori*-associated gastroduodenal ulcers. More recently, a one-week course of an omeprazole-based triple regimen has been reported to have an eradication rate greater than 90%.[21] Drug compliance is an important factor in determining the success of eradication.[7] In this sense, the duration as well as doses of regimens must be further investigated.

Chronic gastritis with *H pylori* infection has various endoscopic appearances, including macroscopically normal mucosa with histologically confirmed inflammation. Antral nodularity is frequently observed especially in children with *H pylori* gastritis.[12–15] Furthermore, many children with *H pylori*-associated duodenal ulcer also have antral nodularity.[18] As previously reported,[12,13,15–17] the present study proved that curing *H pylori* infection reduces the degree of gastric inflammation especially with a reduced number of neutrophils. In addition, the disappearance of antral nodularity was often demonstrated with *H pylori* eradication. On the contrary, Ashorn et al have stressed that the nodularity does not resolve along with active gastritis and persistent nodularity does not indicate persistent *H pylori* infection.[13] The lymphoid follicles with germinal centers demonstrated by histology are probably involved in the pathogenesis of nodularity; however, lymphoid follicles were detectable in some patients in whom the nodularity subsided as evidenced by endoscopy. Although the degree of gastritis is reduced with successful eradication, the inflammatory reaction does not completely disappear in the short-term period after *H pylori* is eradicated. Antral nodularity is a macroscopic marker of *H pylori* infection and its eradication.

There is controversy regarding whether *H pylori* infection is related to symptoms of gastritis/nonulcer dyspepsia.[12–14,16] Our patients with nodular gastritis alone demonstrated different symptom responses to eradication therapy. It was difficult to estimate the response shortly after eradication therapy. The symptomatic efficacy of the bismuth-based regimen may be associated with other mechanisms of bismuth salts (such as cytoprotection) rather than *H pylori* eradication. The role of *H pylori* and its eradication in the symptomatic relief of gastritis/nonulcer dyspepsia remains unclear.

H pylori eradication significantly reduced serum anti-*H pylori* IgG antibody titers; however, many patients continued to be seropositive. It may take more than 6 months after treatment to become seronegative.[14,16,29] A 20% reduction of the IgG antibody titers by 6 months suggests successful eradication therapy, whereas no reduction suggests persistent *H pylori* infection.[30] On the other hand, one study showed a decrease of antibody titers in half of the children with persistent *H pylori* infection.[13] Our data suggests that serial assay of serum anti-*H pylori* IgG antibody titers is useful in long-term monitoring of *H pylori* eradication. At present, however, evidence of eradication should be founded on biopsy-based tests performed at 4 weeks or more after the completion of eradication therapy. In the future, noninvasive urea breath tests may be routinely available in the monitoring of *H pylori* infection. All children with *H pylori*-associated peptic ulcer disease should be treated not only for the ulcer but also for the *H pylori* infection. It is possible that successful eradication means cure of peptic ulcer disease.

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