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Safety and Efficacy of One-Week Triple Therapy for Eradicating *Helicobacter pylori* in Children

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ABSTRACT

Background. Proton pump inhibitor-based eradication therapy of *Helicobacter pylori* has been widely studied in adults, but there have been only a few reports about this therapy in children. The purpose of this study was to investigate the safety and efficacy of 1-week triple therapy for eradication of *H. pylori* and ulcer healing in children.

Patients and Methods. We prospectively studied 15 patients aged 2–17 years (5 with gastric ulcers, 8 with duodenal ulcers, and 2 with nodular gastritis alone). Three patients had H2 blocker-resistant duodenal ulcers. Patients received 0.75 mg/kg of lansoprazole b.i.d., 25 mg/kg of amoxicillin b.i.d., and 10 mg/kg of clarithromycin b.i.d. for 7 days. No additional therapy (including antisecretory drugs) was administered to any patients following eradication therapy. Patients underwent endoscopy to obtain antral biopsies (culture, urease test and histology) and to evaluate the mucosal status, and underwent a ^{13}C-urea breath test before and 4–8 weeks after the completion of a 1-week course of therapy.

Results. All patients received the full drug regimen. Endoscopy showed complete healing of ulcers in 12 of 13 patients with peptic ulcer disease (92%). *H. pylori* was eradicated in 13 of 15 patients (87%). Diarrhea and/or an altered taste sensation occurred in 5 patients (33%). There were no hematological or biochemical abnormalities related to therapy.

Conclusion. The 1-week triple therapy was safe and effective for eradicating *H. pylori*. The present study showed that ulcer healing in juveniles is closely associated with eradication of *H. pylori*, and that no additional therapy is required when *H. pylori* is eradicated. A shorter course of eradication therapy than 2 weeks may be suitable for children with *H. pylori* infection.

Therapy to eradicate *Helicobacter pylori* has been recommended for adults with peptic ulcer disease associated with this organism [1,2]. Infection with *H. pylori* results in chronic infection with rare spontaneous remission. Although the optimal regimen for eradication remains to be established, the combination of a proton pump inhibitor and 1 or 2 antibiotics (so-called new dual/triple therapy) has now replaced the use of bismuth regimens, which was the previous gold standard for eradicating *H. pylori*. Two-week triple regimens including omeprazole are associated with a high rate of eradication of *H. pylori* without severe side-effects in adults [3,4] and in children [5,6]. Successful eradication of the organism significantly reduces the recurrence of peptic ulcer disease [7–9]. Recent studies in adults have shown that reinfection rates range from 0.49% to 4.2% per patient year following eradication therapy [10–14]. Although Rowland et al. reported that children less than 5 years of age are frequently reinfected [15], reinfection rates are relatively low in older children [15,16]. These observations encourage the use of eradication therapy in children with *H. pylori*-associated ulcer disease.

One-week triple regimens containing omeprazole [17–19] or lansoprazole [20,21] are associated with a high eradication rate in adults. In an attempt to identify the optimal eradication strategy in children, we investigated the safety and efficacy of a 1-week triple regimen without any maintenance therapy for eradication of *H. pylori*. In addition, we studied a possible association between *H. pylori* eradication and ulcer healing.

Patients and Methods

We studied 15 *H. pylori*-positive Japanese patients (2–17 years of age) (Table 1). Diagnoses included gastric ulcer in 5 patients, duodenal ulcer in 8 patients, and symptomatic nodular gastritis in 2 pa-

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Table 1 Characteristics of patients with eradication therapy

	Gastric ulcer	Duodenal ulcer	Nodular gastritis
Patients	5	8	2
Mean age, years (range)	7.8 (2–16)	12.3 (5–17)	9.5 (3–16)
Sex (M/F)	3/2	7/1	0/2
Recurrent ulcer	0	6	—
Complications			
Bleeding/visible vessels	4	0	—
Stenosis	0	3	—
Perforation	0	0	—

tients. Symptoms of nodular gastritis were persistent nausea/vomiting for 10 months in a 3-year-old patient and epigastric pain for 15 months in a 16-year-old patient. Upper gastrointestinal series demonstrated normal passage in these two patients; CT scan showed no abnormal findings. Symptoms of ulcer patients included epigastric pain, nausea, tarry stool, and/or hematemesis. Gastric ulcers were newly diagnosed. According to a previously described method [22], local endoscopic injection therapy with pure ethanol was performed in 3 of 4 gastric ulcer patients for visible vessels/active bleeding (Table 1). The success of hemostasis was confirmed endoscopically on the following day. Among 8 patients with duodenal ulcers, 2 patients received eradication therapy at the first presentation of the disease and 6 at the recurrence. In 3 duodenal ulcer patients, the ulcers were resistant to conventional treatment with famotidine or lansoprazole. Duodenal ulcers were accompanied by nodular gastritis in 6 patients. None of the patients had received steroids or nonsteroidal anti-inflammatory drugs. Written informed consent was obtained from all patients and/or their parents.

Treatment Regimen

Doses were based on the results of triple eradication therapy (including a proton pump inhibitor) in adults. The adult dose was divided by 40 kg of body weight. A 7-day course of therapy to eradicate *H. pylori* consisted of lansoprazole 0.75 mg/kg (maximum dose, 30 mg) b.i.d., amoxicillin 25 mg/kg (maximum dose, 1000 mg) b.i.d., and clarithromycin 10 mg/kg (maximum dose, 400 mg) b.i.d. administered after the morning and evening meals. As described above, in 3 patients with duodenal ulcers resistant to famotidine or lansoprazole the antisecretory therapy was followed by eradication therapy. The remaining 12 patients received no medication such as proton pump inhibitors or H2 blockers prior to the eradication therapy. No maintenance therapy of any form was given after the completion of eradication therapy. Assessment of drug compliance was based on the parent's reports.

H. pylori *Tests*

Pretreatment infection with *H. pylori* was confirmed by culture, urease test, and histological examination (hematoxylin-eosin and Giemsa stains) of gastric antral biopsies and determination of serum *H. pylori*-IgG antibody using an enzyme immunoassay [5]. We did not evaluate bacterial resistance to antibiotics. A pretreatment ^{13}C-urea breath test was also performed. Breath samples were collected at baseline, and 10, 20, 30, and 40 min after administration of ^{13}C-urea (3 mg/kg, maximum dose: 100 mg). Based on the results of our biopsy-based tests (culture, urease test, and histology), delta $^{13}C \geq 4.5$ per mil was considered positive for gastric urease activity. If two or more pretreatment tests gave a positive result, the patient was considered to be infected with *H. pylori*. The effect of eradication therapy was evaluated based on upper gastrointestinal endoscopy and biopsies (*H. pylori* culture and histology) and a ^{13}C-urea breath test 4–8 weeks after the completion of therapy. *H. pylori* was considered to be eradicated if all results of these three tests were negative.

Results

H. pylori *Eradication*

Posttreatment tests demonstrated that *H. pylori* was eradicated in 13 of 15 patients (87%). In a 3-year-old patient with nodular gastritis and an 11-year-old patient with duodenal ulcer, *H. pylori* was not eradicated. Side-effects were reported in five patients (33%): diarrhea in three patients, an altered taste sensation in one patient, and diarrhea and an altered taste sensation in one patient. Although loose or watery stools (1–5 times per day) occurred on days 2–4 of eradication therapy in these four patients, the symptoms subsided during therapy or immediately after its completion. Discontinuation of therapy was not required in any patient. All patients received the full drug regimen. Laboratory examinations including white blood cell counts, hemoglobin levels, platelet counts, hepatic and renal function tests, and urinalysis showed no abnormalities after completion of eradication therapy.

Ulcer Healing and Symptomatic Relief

The symptoms disappeared within several days after the initiation of therapy in 12 of 13 ulcer patients. Endoscopy performed 4–8 weeks after com-

pletion of therapy showed complete ulcer healing in these 12 patients (92%). In one duodenal ulcer patient with persistent epigastric pain, in whom eradication failed, the ulcer was unchanged in size four weeks after the therapy. This patient received a two-week course of alternative eradication therapy (lansoprazole 30 mg b.i.d., amoxicillin 1000 mg b.i.d., and metronidazole 375 mg b.i.d.) followed by 30 mg of lansoprazole once-daily for another four weeks. Because it was thought that treatment failure might be associated with a clarithromycin-resistant strain or a short course of the regimen, a two-week course of eradication therapy including metronidazole was chosen. When a six-week course of the therapy ended, both ulcer healing and success of eradication were confirmed. Endoscopy also showed that antral nodularity improved or disappeared in all six patients with successful eradication but did not improve in two patients with eradication failure. The symptoms completely subsided during short-term follow-up in two patients with nodular gastritis alone including the patient with eradication failure.

Before treatment, all patients had histologically moderate to severe gastritis with neutrophil infiltration. After treatment, the number of inflammatory cells in the lamina propria and epithelial infiltration of neutrophils were decreased, indicating a reduction in antral inflammation. However, lymphoid follicles were detected even after the disappearance of antral nodularity.

Discussion

Antimicrobial agents commonly used in proton pump inhibitor-based regimens to eradicate *H. pylori* include amoxicillin, clarithromycin, and metronidazole/tinidazole. Amoxicillin and clarithromycin have a low minimum inhibitory concentration (MIC) against *H. pylori in vitro* [23]. However, because both drugs are maximally effective at a neutral pH, *H. pylori* is difficult to eradicate with monotherapy with amoxicillin or clarithromycin [23,24]. Lansoprazole and omeprazole weakly inhibit *H. pylori* colonization; the MIC of lansoprazole is lower than the MIC of omeprazole [25]. Proton pump inhibitors contribute to the eradication of *H. pylori* mainly by reducing gastric acidity via inhibition of the H^+, K^+ ATPase of parietal cells, thereby enhancing the activity of antibiotics.

It has been suggested that short-term eradication therapy without an antisecretory drug heals gastric ulcers [26] and duodenal ulcers [27]. Our findings support this hypothesis, showing that ulcer healing in children is more closely associated with eradication of *H. pylori* than with lansoprazole-induced gastric acid suppression. Moreover, our results suggest that a major cause of H2 blocker- or proton pump inhibitor-resistant ulcers is *H. pylori* infection. In a 3-year-old patient with eradication failure, dramatic disappearance of the symptom may have been caused by a suppressed infection of *H. pylori* with eradication therapy. Long-term follow-up study is required in this patient.

Previous studies have shown that in children, a 2-week triple regimen of omeprazole, amoxicillin and clarithromycin has an eradication rate of 92% [5]. Also, Dohil et al. reported a 93% success rate with a 2-week regimen containing omeprazole, clarithromycin and metronidazole [6]. Dual drug regimens are associated with eradication rates below 80%, even when administered for 2 weeks and eradication rates vary among studies [3–5]. In the present study, the eradication rates in our one-week regimen were comparable to those obtained in the 2-week regimen used in the previous studies [5,6]. Furthermore, no serious side-effects were found in our study, although the doses of the regimen were about twice as high as the usual clinical doses. Our findings suggest that in children with *H. pylori* infection, a one-week eradication regimen might be a better choice with regard to drug compliance, safety, and cost effectiveness than longer regimens. One-week eradication therapy not only eradicates *H. pylori* but also heals active ulcers. If the ulcer does not heal within 8 weeks after completion of eradication therapy or if symptoms persist, repeat testing for *H. pylori* should be performed as eradication failure may be a cause.

Resistance to antimicrobial agents is an important problem in eradication failure [28]. Metronidazole-resistant strains are common, although the incidence varies between developing and developed countries. Much less than metronidazole, some strains have resistance against clarithromycin [24]. There is a possibility that eradication failure in two patients was related to *H. pylori* strains resistant to clarithromycin. However, we did not examine bacterial resistance to antibiotics. Because clarithromycin is routinely administered to children with various infectious diseases, such as respiratory tract infections, the incidence of resistant strains is expected to increase. Therefore, it may be necessary to replace clarithromycin with another antibiotic in eradication regimens in the future.

A positive *H. pylori* test within 12 months of completion of eradication therapy probably represents recrudescence of a suppressed *H. pylori* in-

fection, not reinfection [29]. There are no highly sensitive tests for the early confirmation of *H. pylori* eradication. To confirm "true" eradication, a ^{13}C-urea breath test should be performed 6–12 months after therapy. In patients with successful eradication, the serum *H. pylori* IgG antibody titer decreases significantly at 1 month after eradication therapy and decreases gradually thereafter [5]. Therefore, a serological test is a useful complementary method for the long-term assessment of *H. pylori* eradication.

References

1 NIH Consensus Conference. *Helicobactor pylori* in peptic ulcer disease. JAMA 1994;272:65–9.
2 Malfertheiner P, Megrand F, O'Morain C, Bell D, Porro B, Deltenre M, et al. Current European concept in the management of *Helicobactor pylori* infection: the Maastricht consensus report. Eur J Gastroenterol Hepatol 1997;9:1–2.
3 Axon ATR, Moayyedi P. Eradication of *Helicobacter pylori:* omeprazole in combination with antibiotics. Scand J Gastroenterol 1996;31(Suppl. 215):82–9.
4 Unge P. Review of *Helicobacter pylori* eradication regimens. Scand J Gastroenterol 1996;31(Suppl. 215):74–81.
5 Kato S, Takeyama J, Ebina K, Naganuma H. Omeprazole-based dual and triple regimens for *Helicobacter pylori* eradication in children. Pediatrics 1997;100:E31–5.
6 Dohil R, Israel DM, Hassall E. Effective 2-week therapy for *Helicobacter pylori* disease in children. Am J Gastroenterol 1997;92:244–7.
7 Coghlan JG, Gilligan D, Humphries H, McKenna D, Dooley C, Sweeney E, et al. *Campylobacter pylori* and recurrence of duodenal ulcers: a 12-month follow-up study. Lancet 1987;2:1109–11.
8 Marshall BJ, Goodwin CT, Warren JR, Murray R, Blincow ED, Blackbourn SJ, et al. Prospective double blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori.* Lancet 1988;2: 1437–42.
9 Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ, Saeed ZA, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. Ann Intern Med 1992;116: 705–8.
10 Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. Gastroenterology 1992;102:41–6.
11 Borody T, Andrews P, Mancuso N, Jankiewicz E, Brandl S. *Helicobacter pylori* reinfection 4 years post-eradication. Lancet 1992;339:1295.
12 Culter AF, Schubert TT. Long-term *Helicobacter pylori* recurrence after successful eradication with triple therapy. Am J Gastroenterol 1993;88:1359–61.
13 Forbes GM, Glaser ME, Cullen DJE, Warren JR, Christiansen KJ, Marshall BJ, et al. Duodenal ulcer treated with *Helicobacter pylori* eradication: seven-year follow-up. Lancet 1994;343:258–60.
14 Bell GD, Powell KU, Burridge SM, Harrison G, Rameh B, Weil J, et al. Reinfection or recrudescence after apparently successful eradication of *Helicobacter pylori* infection: implications for treatment of patients with duodenal ulcer disease. Q J Med 1993;86:375–82.
15 Rowland M, Kumar D, O'Connor P, Daly LE, Drumm B. Reinfection with *Helicobacter pylori* in children (abstract). Gastroenterology 1997;112: A273.
16 Kato S, Abukawa D, Furuyama N, Iinuma K. *Helicobacter pylori* reinfection and ulcer recurrence in children following eradication therapy (abstract). Gastroenterology 1998;114:A170.
17 Bazzoli F, Zagari RM, Fossi S, Pozzato P, Roda A, Roda E. Efficacy and tolerability of a short term, low dose triple therapy for eradication of *H. pylori* (abstract). Gastroenterology 1993;104:A40.
18 Labenz J, Stolte M, Rühl GH, Becker T, Tillenburg B, Sollböhmer M, et al. One-week low-dose triple therapy for the eradication of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1995;7:9–11.
19 Lind T, Veldhuyzen van Zanten S, Unge P, Spiller R, Bayerdörffer E, O'Morain C, et al. Eradication of *Helicobacter pylori* using one- week triple therapies combining omeprazole with two antimicrobials: the MACH 1 study. Helicobacter 1996;1: 138–44.
20 Schütze K, Hentschel E. Duodenal ulcer healing after 7-day treatment: a pilot study with lansoprazole, amoxicillin and clarithromycin. Z Gastroenterol 1995;33:651–3.
21 Harris AW, Pryce DI, Gabe SM, Karim QN, Walker MM, Langworthy H, et al. Lansoprazole, clarithromycin and metronidazole for seven days in *Helicobacter pylori* infection. Aliment Pharmacol Ther 1996;10:1005–8.
22 Kato S, Ozawa A, Ebina K, Nakagawa H. Endoscopic ethanol injection for treatment of bleeding peptic ulcer. Eur J Pediatr 1994;153:873–5.
23 Chiba N, Rao BV, Rademaker JW, Hunt RH. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori.* Am J Gastroenterol 1992;87:1716–27.
24 Peterson WL, Graham DY, Marshall B, Blaser MJ, Genta RM, Klein PD, et al. Clarithromycin as monotherapy for eradication of *Helicobacter pylori:* a randomized, double-blind trial. Am J Gastroenterol 1993;88:1860–4.
25 Bamba H, Kondo Y, Wong RM, Sekine S, Matsuzaki F. Minimum inhibitory concentration of various single agents and the effect of their combinations against *Helicobacter pylori*, as estimated

by a fast and simple *in vitro* assay method. Am J Gastroenterol 1997;92:659–62.
26 Sung JJF, Chung SCS, Ling TKW, Yung MY, Leung VKS, Ng EKW, et al. Antibacterial treatment of gastric ulcers associated with *Helicobacter pylori*. N Engl J Med 1995;332:139–42.
27 Hosking SW, Ling TKW, Chung SCS, Yung MY, Cheng AFB, Sung JJY, et al. Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial. Lancet 1994;343:508–10.
28 De Boer WA, Tytgat GNJ. The best therapy for *Helicobacter pylori* infection: should efficacy or side-effect profile determine our choice? Scand J Gastroenterol 1995;30:401–7.
29 Bell GD, Powell KU. *Helicobacter pylori* reinfection after apparent eradication: the Ipswich experience. Scand J Gastroenterol 1996;31(Suppl. 215): 96–104.