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Results of triple eradication therapy in Japanese children: a retrospective multicenter study

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Background. Large-scale clinical trials in children are lacking concerning *Helicobacter pylori* eradication therapies. The purpose of this study was to assess the efficacy of proton pump inhibitor (PPI)-based triple therapies in Japanese children. ***Methods.*** This was a retrospective analysis of the first- and second-line PPI-based triple therapies from pediatric gastrointestinal units between 1996 and 2003. Data collected included doses and duration of regimens, drug compliance, success or failure of eradication, ulcer healing, and symptom response of those with dyspepsia and no ulcers. The results of antibiotic susceptibility tests were also reported in cases where these were performed. ***Results.*** A total of 149 pediatric patients (mean age, 12.6 years) were studied, including 123 patients who received first-line therapy: 115 received a PPI plus amoxicillin and clarithromycin (PAC) and 8 received a PPI plus amoxicillin and metronidazole (PAM). Overall eradication rates of the first-line PAC and PAM therapies were 77.4% and 87.5%, respectively ($P = 0.68$). All 14 patients with failed PAC therapy received the second-line PAM regimen, resulting in an eradication rate of 100%. Mild side effects were reported only in PAC regimens (13.8%). Primary resistance to amoxicillin, clarithromycin, and metronidazole was detected in 0%, 34.7%, and 12.5% of the strains, respectively. The PAC regimen showed a high eradication rate for clarithromycin-susceptible strains (91.7%), but was relatively ineffective for resistant strains (40.0%) ($P < 0.01$). Eradication of *H. pylori* was associated with ulcer healing and symptomatic improvement among those with gastritis only (both; $P < 0.001$). Among 17 patients with iron-deficiency anemia, post-treatment hemoglobin levels were higher than the pretreatment levels ($P < 0.001$). ***Conclusions.*** The PAC regimen is effective in children. Clarithromycin resistance is associated with eradication failure. Metronidazole is a good substitute for clarithromycin as the second-line option for children.

Key words: child, clarithromycin, eradication therapy, *Helicobacter pylori*, metronidazole

Introduction

Triple therapies consisting of a proton pump inhibitor (PPI) and two antibiotics have been shown to be effective for eradicating *Helicobacter pylori* in children.[1–4] The Canadian *Helicobacter* Study Group,[5] the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN),[6] and the Japanese Pediatric *Helicobacter* Study Group[7] have all recommended these triple therapies, using amoxicillin, clarithromycin, or metronidazole as the first-line option for *H. pylori* eradication. The Japanese Study Group did not recommend metronidazole,[7] because this drug has been approved by the Japanese national health insurance system only for use for trichomoniasis. Despite the recommendations of these leaned societies, large-scale trials of the efficacy of PPI-based triple eradication therapy in children are generally lacking. Furthermore, *H. pylori* resistance to antibiotics, especially clarithromycin, has been a growing problem.[8] The purpose of this study was to assess the efficacy and safety of PPI-based triple therapies in Japanese children. The influence of clarithromycin resistance on eradication success, ulcer healing, and clinical symptoms was also evaluated.

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Methods

PPI-based triple eradication therapies in children were retrospectively evaluated. Questionnaires were sent to eight pediatric departments where eradication therapy has been actively performed in Japan. All patients who underwent upper gastrointestinal endoscopy and were treated with triple therapies consisting of a PPI and two antibiotics (e.g., amoxicillin plus clarithromycin or amoxicillin plus metronidazole) between January 1996 and March 2003 were entered. Data collected included: age, sex, and *H. pylori* presentation; doses and duration of PPI and antibiotics used; drug compliance; side effects; success or failure of eradication; ulcer healing; and finally, change in symptoms in relation to eradication. The results of antibiotic susceptibility testing (minimal inhibitory concentrations [MICs]), if performed, were also reported.

Pre- and post-treatment confirmation of *H. pylori* status was based on combinations of culture, rapid urease test, histology, ^{13}C-urea breath test, and stool antigen test (Premier Platinum HpSA; Meridian Bioscience, Cincinnati, OH, USA). The cutoff value of the ^{13}C-urea breath test was 3.5‰.[9] According to the manufacturer's instructions, the results of the stool antigen test were defined as negative, positive, and indeterminate, respectively.[10] If one test or more were positive, the patients were judged to be infected with *H. pylori*. If all tests performed were negative, the patients were judged to be not infected with *H. pylori*. In nonulcer patients, symptomatic responses to *H. pylori* eradication were divided into complete disappearance, partial improvement, no response, and unknown.

Statistical analyses were done using the unpaired Student's *t*-test or the χ^2 test. Values were expressed as means (±SD) or medians. A P value of <0.05 was considered significant.

Results

Patients and confirmation of H. pylori *status*

A total of 149 patients, aged 1 to 18 years (mean, 12.6 years) were entered (Table 1). The first-line therapy was done in 123 patients and second-line therapy in 26. For pretreatment diagnosis of *H. pylori* infection, 145 patients (97.3%) had two or more tests, including biopsy tests. Two or three biopsy specimens were taken from the gastric antrum. Histological examination alone and a combination of ^{13}C-urea breath test and stool antigen test were performed in 1 and 3 patients, respectively. Similarly, 111 patients (74.5%) underwent two tests or more, including biopsy tests, for the assessment of *H. pylori* eradication. Among the remaining 38 patients, either ^{13}C-urea breath test alone ($n = 29$) or a combination of ^{13}C-urea breath test and stool antigen test ($n = 9$) was done. None of the patients had received PPIs or antibiotics such as clarithromycin for 4 weeks prior to the endoscopy and *H. pylori* testing. Post-treatment *H. pylori* testing was performed at a median of 8 weeks (range, 4 to 56 weeks) after eradication therapy was completed. In 83% (124 patients), testing was performed 8 to 12 weeks after the completion of eradication therapy. Informed consent for eradication therapy was obtained from the patients or their parents.

First-line eradication therapy

Among the 123 patients with first-line therapy, 115 patients received regimens with amoxicillin and clarithromycin (PAC) and 8 patients received those with amoxicillin and metronidazole (PAM; Table 2). Duration of the eradication therapy was 7, 10, or 14 days. The PPIs used included lansoprazole ($n = 100$), omeprazole ($n = 21$), rabeprazole ($n = 1$), and pantoprazole ($n = 1$). Doses of lansoprazole and omeprazole ranged between 1.0 and 1.5 mg/kg per day (maximum, 60 mg/day) and between 1.0 and 1.3 mg/kg per day (maximum, 40 mg/day), respectively. Doses of amoxicillin, clarithromycin, and metronida-

Table 1. Summary of patients with first-line and second-line PPI-based triple therapy

Disease	No. of patients (male)		
	First-line	Second-line	Total
Total	123 (77)	26 (19)	149 (96)
Gastritis	60 (28)	10 (5)	70 (33)
Duodenal ulcer	38 (33)	12 (10)	50 (43)
Gastric ulcer	9 (6)	1 (1)	10 (7)
Fe-deficiency anemia	14 (9)	3 (3)	17 (12)
Other	2 (1)[a]	0 (0)	2 (1)

[a] Idiopathic thrombocytopenic purpura, 1; urticaria, 1

Table 2. Eradication rates of first-line PPI-based triple therapies

	Amoxicillin + clarithromycin				Amoxicillin + metronidazole	
Duration	7 Days	10 Days	14 Days	Overall	7–14 Days	*P* value[a]
No. of patients	50 (48)	23 (23)	42 (4)	115 (112)	8 (8)	
Eradication (%)	70.0 (72.9)	87.0 (87.0)	81.0 (82.9)	77.4 (79.5)	87.5 (87.5)	0.68

The numbers in parentheses represent data of patients with drug compliance of 90% or more
[a] Regimens with amoxicillin + clarithromycin versus those with amoxicillin + metronidazole

Table 3. Eradication rates of second-line PPI-based triple therapies

	Amoxicillin + clarithromycin		Amoxicillin + metronidazole		Amoxicillin + others[a]	
First-line antibiotics	*n*	Eradication (%)	*n*	Eradication (%)	*n*	Eradication (%)
Amoxicillin[b]	3	100				
Clarithromycin[b]	3	66.7			1	100
Amoxicillin + clarithromycin	3	66.7	14	100	1	100
Amoxicillin + metronidazole					1	100
Overall	9	77.8	14	100	3	100

[a] "Others" includes minocycline, levofloxacin, and faropenem
[b] PPI dual therapy

zole were 40 to 60 mg/kg per day (maximum, 2000 mg/day), 20 to 24 mg/kg per day (maximum, 1000 mg/day), and 10 to 20 mg/kg per day (maximum, 1000 mg/day), respectively. In 70% of ulcer patients ($n = 42$), either a PPI or a histamine 2 (H2) receptor blocker alone was administered until endoscopy was repeated after eradication therapy. Drug compliance was over 90% in 98.0% of patients.

Overall eradication rates for the PAC and PAM regimens were 77.4% and 87.5%, respectively ($P = 0.68$; Table 2). There were no significant differences in the eradication rates among the 7-, 10-, and 14-day course regimens (*P* values not shown).

Second-line eradiation therapy

Of the 26 patients who received second-line therapies, 9 and 14 patients received second-line therapies of the PAC and PAM regimens, respectively (Table 3). Of the remaining 3 patients, 1 patient each received a PPI and amoxicillin plus minocycline, levofloxacin, or faropenem. The duration of the therapy was 7 or 14 days. The drug compliance was 100% in all patients. The overall eradication rate of the second-line PAC therapy was 77.8%: in patients who failed first-line therapy that included clarithromycin (PAC therapy or dual therapy consisting of a PPI and clarithromycin), the eradication rate was 66.7%. On the other hand, PAM therapy was done in 14 patients with unsuccessful PAC therapy and the eradication rate was 100%. *H. pylori* eradication was also successful in the 3 patients who received a PPI, amoxicillin, and either minocycline, levofloxacin, or faropenem.

Side effects

Side effects were reported in 13.8% of patients with PAC therapy. During eradication therapy, diarrhea, taste disturbance, nausea, and skin rash occurred in 8.9%, 4.8%, 1.6%, and 0.1% of patients, respectively. However, the symptoms were mild and the therapy was not stopped in any patients. There were no side effects reported in patients with PAM or other regimens.

Antimicrobial susceptibility

The MICs of *H. pylori* strains to amoxicillin, clarithromycin, and metronidazole were reported in 72 patients with the first-line therapy and in 7 patients with second-line therapy. Among these patients, the MICs were examined using a microdilution method[8] ($n = 49$) or an agar dilution method ($n = 23$). The methods of testing were unknown in 7 patients. Resistance breakpoints for amoxicillin, clarithromycin, and metronidazole were defined as >0.5, ≥ 1.0, and >8.0 mg/l, respectively.[8] Primary resistance to amoxicillin, clarithromycin, and metronidazole was detected in 0%, 34.7%, and 12.5% of the strains, respectively. Secondary resistance to amoxicillin and clarithromycin was detected in 0% and 57.1% of the strains, respectively.

Table 4. Eradication rates of PPI-based triple therapies is clarithromycin-susceptible and resistant strains

	Total	Susceptible	Resistant	*P* value[a]
Amoxicillin + clarithromycin				
No. of strains	68	48	20	
Eradication rate (%)	76.5	91.7	40.0[b]	<0.01
Amoxicillin + metronidazole				
No. of strains	12	3	9	
Eradication rate (%)	91.7	100	88.9[b]	Not applicable

[a] Clarithromycin-susceptible versus resistant strains
[b] $P < 0.05$

Table 5. *Helicobacter pylori* eradication and symptom response in nonulcer patients

		Eradication		
Symptom response	No. of patients	Success	Failure	*P* value[a]
Complete disappearance	40	37	3	
Partial improvement	18	16	2	
No response	7	1	6	<0.001
Unknown	5	2	3	
Total	70	56	14	

[a] Patients with complete disappearance of symptoms or partial improvement versus those without any response; $P < 0.05$ for patients with complete disappearance of symptoms versus those with partial improvement or no response

The eradication rate of the PAC regimen was higher in clarithromycin-susceptible strains (91.7%) than in resistant strains (40.0%; $P < 0.01$; Table 4). As expected, the PAM regimen showed high eradication rates independent of clarithromycin susceptibility. In clarithromycin-resistant strains, the eradication rate of the PAC regimen (40.0%) was reduced compared to the PAM regimen (88.9%; $P < 0.05$).

Ulcer healing and symptomatic effects

In patients with duodenal ($n = 48$) and gastric ulcers ($n = 10$), follow-up endoscopy was performed at a median of 8 weeks (6 to 18 weeks) after the completion of eradication therapy. At follow-up endoscopy, the healing rate of duodenal ulcers was significantly higher in patients with successful eradication (100%) than in those with eradication failure (44.4%; $P < 0.001$). Gastric ulcers healed in 9 patients with successful eradication, but did not heal in 1 patient with eradication failure ($P = 0.10$).

Symptom responses to eradication therapy were reported in 65 patients with *H. pylori* gastritis (Table 5). Compared to the patients without any response, successful *H. pylori* eradication significantly improved the symptoms ($P < 0.001$; Table 5). There was also a significant difference between the patients with complete disappearance of symptoms and those with partial symptom improvement or no response ($P < 0.05$).

Among the 17 patients with iron-deficiency anemia, *H. pylori* was eradicated in 14 patients and not eradicated in 3 patients. In 10 out of the 14 patients with successful eradication, pre- and post-treatment peripheral hemoglobin levels were reported. Use of iron supplement therapy was not questioned. The poststreatment hemoglobin levels (8.5 ± 1.5 g/dl) were significantly increased compared with the pretreatment levels (12.6 ± 1.1 g/dl; $P < 0.001$).

Discussion

This study has demonstrated that PAC triple therapy is reasonably effective as the first-line eradication therapy in most Japanese children with *H. pylori* infection. Overall, the variations in doses of PPIs (lansoprazole or omeprazole), amoxicillin, and clarithromycin were small, possibly because most pediatricians followed the recommendations of the Japanese guidelines for children.[7] Primary resistance to clarithromycin has been frequently observed, with the rate being 29% in *H. pylori* isolates from children, and resistance was associated with eradication failure.[8] An increasing rate of clarithromycin resistance has also been reported in Japanese adults.[11,12] In Japan, clarithromycin has been widely used in the pediatric patient population, and its recent market share accounts for more than 10% of the oral antibiotics administered to children.[8] In a Portu-

guese study,[13] clarithromycin resistance was more prevalent among *H. pylori* isolates from children than among those from adults.

The PAM regimen was effective, with a high eradication rate irrespective of clarithromycin resistance. In one children's study,[14] the first-line PAM regimens showed an overall eradication rate of 83%. In Japanese adults who failed PAC therapy, eradication rates with a PAM regimen were more than 80%,[15,16] and the Japanese Society of *Helicobacter* Research has recommended the PAM regimen as the second-line option in the revised guidelines in 2003. Although an association between metronidazole and lung-cancer risk is under debate,[17,18] the PAM regimen was effective even for metronidazole-resistant *H. pylori* isolates.[16]

With regard to the second-line options for children with eradication failure, the NASPGHAN has recommended a quadruple regimen, consisting of bismuth subsalicylate, a PPI, metronidazole, and an additional antibiotic (amoxicillin, tetracycline, or clarithomycin) or a combination of ranitidine, bismuth citrate, clarithromycin, and metronidazole.[6] In Japan, however, bismuth compounds are not clinically available,[16] making the PAM regimen the preferred second-line option for children who fail eradication therapies containing clarithromycin.

In the present study, eradication of *H. pylori* was closely associated with duodenal ulcer healing. Successful *H. pylori* eradication significantly reduced ulcer recurrence in children.[19] In addition, the reinfection rate after successful eradication in children older than 5 years was low, with the rate being 2.0%[20] or 2.4% per person per year.[19] The present study also suggested that *H. pylori* eradication improved gastrointestinal symptoms in the infected children. While it remains controversial whether *H. pylori* infection is associated with gastrointestinal symptoms such as abdominal pain in children,[4,21,22] the Canadian *Helicobacter* Study Group[5] and the European Pediatric Task Force on *Helicobacter pylori*[23] have both recommended that *H. pylori* eradication therapy be considered if a child undergoes endoscopy and the infection is identified. Our data support these recommendations, but controlled trials will be needed to confirm this hypothesis.

Many recent studies have reported that *H. pylori* causes iron-deficiency anemia in a subset of infected persons,[24,25] although the mechanism of this complication is not fully understood. From the results of the present study, it is suggested that *H. pylori*-infected children with iron-deficiency anemia should be treated for the infection as well as the iron deficiency.

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