

## Evaluation of Therapeutic Regimens for the Treatment of *Helicobacter pylori* Infection

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*Helicobacter pylori* (*H. pylori*) is currently considered the most important exogenous factor in the genesis of gastritis and peptic ulcer disease. However, the optimum regimen for the eradication of *H. pylori* remains unclear. The purpose of this study was to evaluate the eradication rate of *H. pylori*, the side effects, and the patients' compliance with regard to various drug regimens. We also analyzed factors influencing the eradication of *H. pylori*. One hundred and eighty patients were included and divided into four groups: 42 patients (Group 1) received tripotassium dicitrate bismuthate (240 mg b.i.d.), metronidazole (250 mg t.i.d.) and amoxicillin (500 mg t.i.d.) for 14 days; 55 patients (Group 2) received omeprazole (20 mg b.i.d.) and amoxicillin (1000 mg b.i.d.) for 14 days; 36 patients (Group 3) were treated with omeprazole (20 mg b.i.d.), metronidazole (250 mg t.i.d.) and amoxicillin (500 mg t.i.d.) for 14 days; and 47 patients (Group 4) received omeprazole (20 mg q.d.) and amoxicillin (500 mg t.i.d.) for 14 days and then tripotassium dicitrate bismuthate (240 mg b.i.d.) and nizatidine (150 mg q.d.) for 14 days. The diagnosis of *H. pylori* was made by histology. The eradication of *H. pylori* was defined both by histology (H&E and Giemsa stain) and by rapid urease test (CLO<sup>+</sup>) showing negative for *H. pylori* 4 weeks after the completion of therapy. Of the 180 patients, 95 patients had non-ulcer dyspepsia, 40 patients had gastric ulcer and 45 patients had duodenal ulcer. The eradication rate of *H. pylori* was highest (89.3%) in Group 3, as compared with Group 1 (68.9%), Group 2 (65.4%), and Group 4 (48.9%). The eradication rate was significantly higher in Group 3 than in Groups 2 and 4 ( $p < 0.05$ ). There was no significant difference in the eradication rate among clinical diagnosis, sex and age. But, in the conventional triple therapy (Group 1), the eradication rate was higher in male (78.6%) than in female (46.2%). The side effects, in order, were nausea (22.1%), dizziness (19.5%), abdominal pain (11.6%) and diarrhea (9.7%), and there was no difference among the drug regimens. The compliance of the patients was good (more than 80% irrespective of drug regimen). On the basis of these findings, the side effects of the drugs seemed minimal, and the compliance of patients was good irrespective of the drug regimen. In conclusion, the triple therapy with omeprazole, metronidazole and amoxicillin was the most effective regimen and could be recommended for *H. pylori* eradication.

**Key Words:** *Helicobacter pylori* infection, drug regimen, eradication

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*Helicobacter pylori* (*H. pylori*) is a gram-negative, motile, microaerophilic, curved bacillus that is found in the mucus layer overlying the gastric epithelium (Warren and Marshall, 1983). *H. pylori* infection has been recognized as the primary cause of chronic gastritis and peptic ulcer disease (Sipponen *et al.* 1989; Nomura *et al.* 1994). In addition, there is growing

evidence that *H. pylori* is a pathogenic factor in some gastric cancers and lymphomas (Wotherspoon *et al.* 1991; Hansson *et al.* 1993). In the United States, *H. pylori* may be found in the gastric mucosa of 50 percent of the population by age 55 (Dooley *et al.* 1989), and in Korea, about 80 percent of asymptomatic persons have been documented *H. pylori* positive by serologic tests (Park *et al.* 1995). *H. pylori* was found in 70~90% of chronic gastritis, 57~90% of gastric ulcer, and 80~90% of duodenal ulcer patients (Kang *et al.* 1991; Goldschmiedt and Peterson, 1993; Chang *et al.* 1994).

*H. pylori* is sensitive to a wide variety of antibiotics in vitro, but when used on their own in vivo the results have been uniformly disappointing (Northfield *et al.* 1993). Numerous agents have been evaluated in the treatment of *H. pylori* infection, including bismuth compounds, amoxicillin, tetracycline, clarithromycin, metronidazole, omeprazole, and histamine-2 receptor blocker, singly or in various combinations (Heatley, 1992; Labenz *et al.* 1993; Bell *et al.* 1995). However, the optimum drug regimen for the eradication of *H. pylori* remains unclear. To the best of our knowledge, there have been no comparative studies with regard to various drug regimens in Korea.

The purpose of this study was to evaluate the eradication rate of *H. pylori*, the side effects of drugs and the patients' compliance with regard to various drug regimens. We also analyzed the factors influencing the eradication of *H. pylori*.

## MATERIALS AND METHODS

### Materials

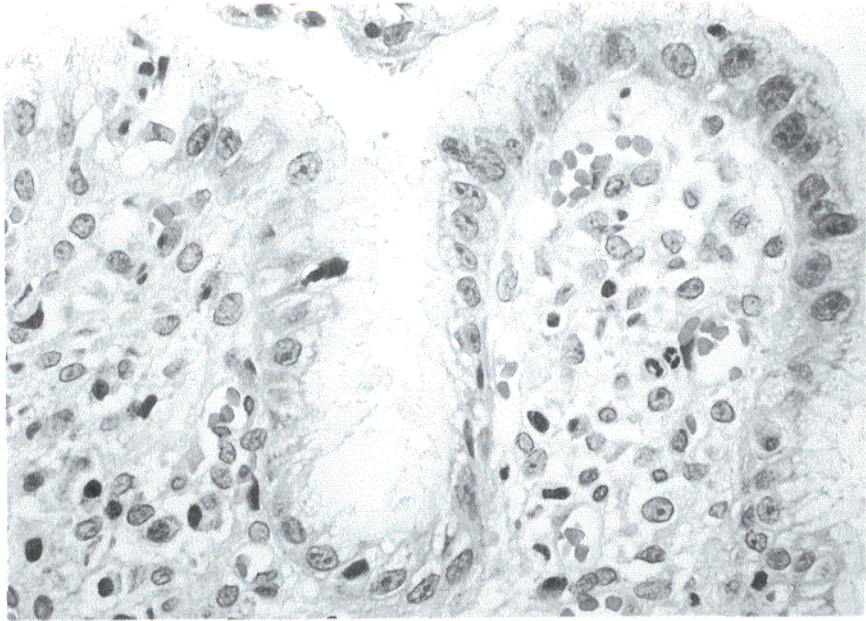
One hundred and eighty patients who visited the Severance Hospital from January to August, 1995, and received *H. pylori* (+) confirmation through endoscopic biopsy, were included in the study. Three biopsy specimens were taken from the antrum within 3 cm of the pylorus: one for the Hematoxyline-Eosin (H&E) stain (Fig. 1), one for the Giemsa stain (Fig. 2), and one for the rapid urease test (CLO<sup>R</sup>, Delta West Pty Ltd. Bentley, W. Australia).

Table 1. Drug regimens according to group

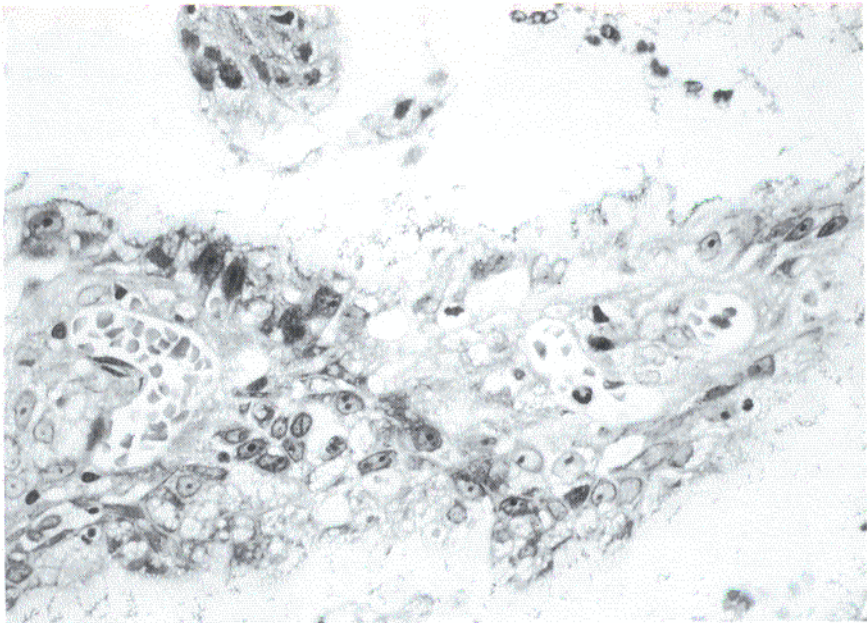
Group	Drugs	Dosage	Duration (days)
Group 1 (GMA)	CBS(Denol <sup>®</sup> )	240 mg b.i.d.	14
	Metronidazole	250 mg t.i.d.	
	Amoxicillin	500 mg t.i.d.	
Group 2 (OA)	Omeprazole	20 mg b.i.d.	14
	Amoxicillin	1000 mg b.i.d.	
Group 3 (OAM)	Omeprazole	20 mg b.i.d.	14
	Amoxicillin	500 mg t.i.d.	
	Metronidazole	250 mg t.i.d.	
Group 4 (OAB)	Omeprazole	20 mg p.d.	14
	Amoxicillin, than	500 mg t.i.d.	
	Nizatidine	150 mg p.d.	14
	CBS(Denol <sup>®</sup> )	240 mg b.i.d.	

### Drug regimens (Table 1)

The patients were divided into four groups: 42 patients (Group 1) received tripotassium dicitrato bismuthate (240 mg b.i.d.), metronidazole (250 mg t.i.d.) and amoxicillin (500 mg t.i.d.) for 14 days; 55 patients (Group 2) received omeprazole (20 mg b.i.d.) and amoxicillin (1000 mg b.i.d.) for 14 days; 36 patients (Group 3) were treated with omeprazole (20 mg b.i.d.), metronidazole (250 mg t.i.d.) and amoxicillin (500 mg t.i.d.) for 14 days; and 47 patients (Group 4) received omeprazole (20 mg q.d.) and amoxicillin (500 mg t.i.d.) for 14 days and then tripotassium dicitrato bismuthate (240 mg b.i.d.) and nizatidine (150 mg q.d.) for 14 days. Four weeks after the completion of therapy, follow-up endoscopy was performed, and the eradication was defined when negative conversion of *H. pylori* was proved both by histology (H&E and Giemsa stain) and by the rapid urease test. Before treatment, patients were given information on the basic concepts of the pathophysiology of *H. pylori* infection. The patients were advised to complete the entire course of therapy and to report any side effects of treatment. Their compliance was expressed as the ratio of the amount of drugs taken/the amount of prescribed drugs.



**Fig. 1.** H&E stain of gastric mucosa shows surface foveolar cells, adherent mucus, and scattered bacillary forms within the mucus.



**Fig. 2.** Giemsa stain shows abundant bent, rod-shaped organisms in the superficial mucus layer.

**Statistics**

Descriptive statistics and the chi-square test with Yates correction have been used to compare and contrast the different treatment groups. Factors affecting the eradication rate were analysed by multiple logistic regression.

**RESULTS**

A total of 110 men and 70 women were studied, with median age of 49 years. Of the 180 patients, 95 had non-ulcer dyspepsia (NUD), 40 had gastric ulcer (GU), and 45 had duodenal ulcer (DU). There were no differences in diagnosis, age and gender distributions among the drug regimens (Table 2). The eradication rate of *H. pylori* was highest (89.3%) in Group 3 (triple therapy including omeprazole),

followed by 68.9% in Group 1 (conventional triple therapy), 65.4% in Group 2, and 48.9% in Group 4. The eradication rate was significantly higher in Group 3 as compared with Groups 2 and 4, respectively ( $p < 0.05$ ) (Fig. 3). The eradication rate for the DU patients was 74.1%, 67.7% for the GU patients, and 62.1% for the NUD patients, but there was no significant difference in clinical diagnosis among these groups (Fig. 4). Also, no significant differences were seen in the eradication rate with regard to sex and age, with the exception that in conventional triple therapy (Group 1), the eradication rate was higher in men (78.6%) than in women (46.2%) (Fig. 5). The most common side effects were nausea (22.1%), dizziness (19.5%), abdominal pain (11.6%) and diarrhea (9.7%), in that order, and there were no differences in the distribution of these side effects among the drug regimens (Table 3).

The patient compliance was good (over 80

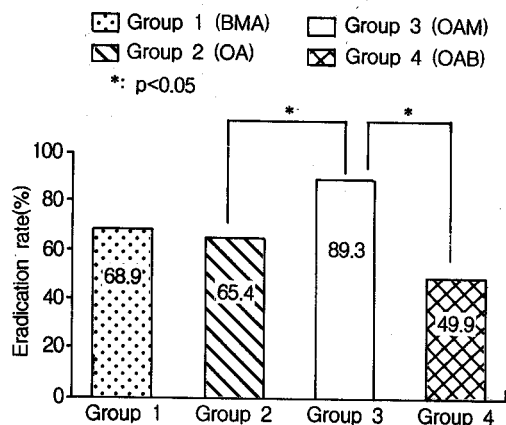


Fig. 3. Eradication rate according to drug regimen.

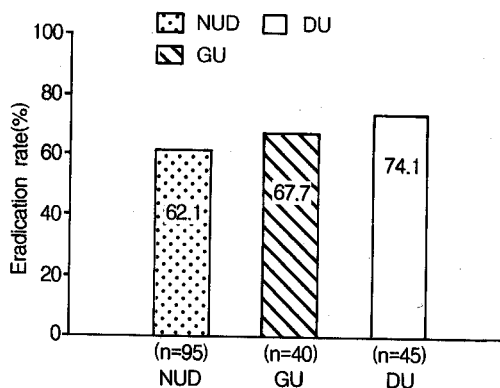


Fig. 4. Eradication rate according to diagnosis.

Table 2. Clinical characteristics of patients

	Group 1 (BMA)	Group 2 (OA)	Group 3 (OAM)	Group 4 (OAB)
No. of patients	42	55	36	47
Age (mean, yrs)	43	50	49	51
Sex (M/F)	26/16	35/20	21/15	28/19
NUD/GU/DU	24/9/9	25/14/16	18/8/10	28/9/10

NUD: Non ulcer dyspepsia,  
GU: Gastric ulcer, DU: Duodenal ulcer

Table 3. Side effects according to therapeutic regimen(%)

Side effects	Group 1 (BMA)	Group 2 (OA)	Group 3 (OMA)	Group 4 (OAB)	Total
Nausea	27.5	18.7	20.4	21.5	22.1
Dizziness	23.1	18.8	19.0	17.4	19.5
Abdominal pain	12.6	10.5	11.5	11.8	11.6
Diarrhea	11.9	8.5	9.7	9.0	9.7
Metallic taste	11.0	0	10.5	0	5.6

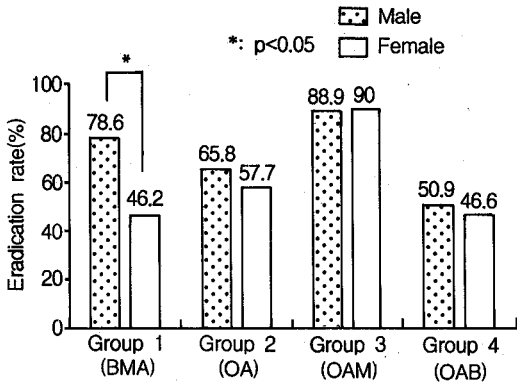


Fig. 5. Eradication rate according to sex in each drug regimen.

%), irrespective of the drug regimen. The only factor affecting the eradication rate of *H. pylori* appeared to be the type of drug regimen used.

## DISCUSSION

*H. pylori* colonization of the gastric mucosa is now being recognized to be strongly associated with both chronic active gastritis and peptic ulcer disease (Sato *et al.* 1991; Sipponen and Hyvarinen, 1993). Indeed, infection with *H. pylori* have been found to be associated with a greatly increased risk of duodenal and gastric ulceration: from 95 to 100% of patients with duodenal ulcer and 75-85% of patients with gastric ulcer (Wyatt and Dixon, 1990; Nomura *et al.* 1994). In Korea, similar association has been reported (Kang *et al.* 1991; Chang *et al.* 1994). The most compelling evi-

dence in support of the role of *H. pylori* in the pathogenesis of peptic ulcer disease is the repeated demonstration that 1-year relapse rates for duodenal ulcer treated with histamine-2 receptor xxxantagonists are 70 to 80 percent, compared with less than 20 percent for duodenal ulcers given therapy aimed at the eradication of *H. pylori* (Graham *et al.* 1992a; Lambert *et al.* 1995). In the NIH consensus, the eradication therapy of *H. pylori* has been recommended in patients with peptic ulcer disease associated with *H. pylori* (NIH consensus conference, 1994).

Although *H. pylori* is the primary cause of gastritis and the essential factor in the pathogenesis of peptic ulcer disease, it has not been proven to play a role in the pathogenesis of NUD (Greenberg and Bank, 1990). Recent studies suggest that about 50 percent of patients with NUD are infected with *H. pylori*, but there is still no convincing evidence that *H. pylori* accounts for the symptoms in these patients (Elta *et al.* 1995). The value of treatment of NUD with *H. pylori* infection remains to be determined.

In the present study, we used eradicating regimens in patients with *H. pylori* associated NUD but the improvement of dyspeptic symptoms were not evaluated and further study is required.

In vitro, *H. pylori* is highly sensitive to a wide variety of antibiotics, but when used on their own in vivo, the results have been uniformly disappointing (Northfield *et al.* 1993). This disparity may be due to the decreased effectiveness of antibiotics in the acidic milieu of gastric mucosa. Numerous agents have been evaluated for the treatment of *H. pylori* infection, including bismuth compounds, amoxi-

cillin, tetracycline, clarithromycin, metronidazole, and omeprazole in various combinations, and many authors have recommended combination therapy for 14 days (Heatley, 1992; Northfield *et al.* 1993). The mechanism of action of bismuth is uncertain but may involve cytoprotective effects, including binding to the ulcer base, and stimulation of mucus and prostaglandin production. In addition, bismuth is thought to exert an antibacterial effect through the inhibition of proteolytic, lipolytic, and urease enzyme activity. When used alone, bismuth compounds result in the eradication of *H. pylori* in only 20 percent of the patients, but when used in combination with antibiotics, they could eradicate *H. pylori* in up to 90% of the patients (Heatley, 1992; Jacques and Lawrence, 1994).

Conventional triple therapy, combining bismuth compounds, amoxicillin and metronidazole, has been reported as the best regimen, but this regimen has problems such as considerable side effects, lack of compliance and metronidazole resistance. The incidence of side effects has been reported to be as high as 63.2% (Northfield *et al.* 1993). In conventional triple therapy, eradication was achieved in about 91% of the patients with metronidazole sensitive organisms, whereas only 63% was achieved with metronidazole resistant organisms (Rautelin *et al.* 1992). The high incidence of metronidazole resistance in *H. pylori* infections of the developing countries is the result of the widespread use of this drug for diarrheal or gynecologic diseases (Northfield *et al.* 1993). In the present study, the eradication rate of the conventional triple therapy (Group 1) was 68.9% which was lower than those previously reported. The eradication rate of 62.5% reported in a previous study in Korea was similar to our results (Choi and Chung, 1994). This low eradication rate in Korea may be due to metronidazole resistance, and this assumption was supported by the higher eradication rate in men (78.6%) than in women (46.2%) due to more previous use of metronidazole in women. Further evaluation on the metronidazole resistant strains thus deemed to be necessary.

The requirement for acid suppression in

addition to therapy aimed at eradicating *H. pylori* has been questioned. The observation that omeprazole reduces *H. pylori* colonization led to experiments with combinations of antibiotic therapy and omeprazole (Bayerdorffer *et al.* 1992; Unge *et al.* 1992). It has also been reported that a 14-day regimens were more effective than those of 7~10 days (Labenz *et al.* 1993). There is still no satisfactory explanation for the much greater efficacy of a combined omeprazole/antibiotic treatment regimen. Omeprazole alone acts bacteriostatically on *H. pylori* in vitro, but its in vivo mechanism of action is still unknown. Omeprazole monotherapy was found to merely suppress bacterial colonization, especially in the antral lesion. It seems more likely that a decisive factor is the improvement in the antibacterial activity of the antibiotics after profound inhibition of acid secretion. In addition, therapeutically induced hypoacidity may result in bacterial overgrowth of the stomach, with consecutive displacement of *H. pylori* (Northfield *et al.* 1993; Labenz and O'Morain, 1995). The eradication rate of omeprazole with amoxicillin was variable at 50-90%. The most promising result seems to be associated with a twice-daily dose of omeprazole which produces a better pH control over 24 hours. In the present study, the eradication rate of 40 mg omeprazole (65.4%) was higher than the 20 mg regimen (48.9%). Thus, twice-daily dose of omeprazole was recommended in the regimen of omeprazole/antibiotics. The advantage of this dual regimen over triple therapy is that there are fewer side-effects, and that metronidazole resistance is not a problem (Heatley, 1992; Labenz *et al.* 1993). Recently, clarithromycin, a new macrolide antimicrobial agent, has widely been used in dual therapy in place of amoxicillin, and has demonstrated a high eradication rate of over 80% (Logan *et al.* 1994). The study of the efficacy of omeprazole/clarithromycin is an ongoing project in our institute.

The new triple therapy with omeprazole, amoxicillin and metronidazole has shown promising results achieving high eradication rates of up to 85-90%. This combination has such advantages as short-course therapy (7

days) and high efficacy in metronidazole-resistant strains (Bazzoli *et al.* 1994; Bell *et al.* 1995; Hudson *et al.* 1995). Bell *et al.* (1995) reported that the eradication rate of this combination was more than 80%, and claimed that the use of omeprazole overcomes most of the effects of bacterial resistance to metronidazole. In our study this combination therapy showed the highest eradication rate, and there were no differences between men and women unlike the group treated with the traditional triple therapy. These results suggested that omeprazole may overcome the resistance to metronidazole.

Although the incidence of the individual side effects was rather high, they were generally mild. In our study, the side effects were nausea (22.1%), dizziness (19.5%), abdominal pain (11.6%) and diarrhea (9.7%), in order, and there were no differences among drug regimens. No patients discontinued the medication due to side effects.

Graham *et al.* (1992b) reported that the patients' compliance was the single most important factor in the eradication rate. Thijs *et al.* (1993) claimed the importance of pretreatment instructions in completing the eradication therapy. We found high patient compliance rates irrespective of drug regimen in our study, and this was most likely due to the pretreatment instructions stressing the importance of therapy and the mild degree of side effects.

In summary, the side effects of the drugs were thought as minimal, and the patient compliance was good irrespective of drug regimen. The triple therapy with omeprazole, metronidazole and amoxicillin was the most effective regimen and could be recommended for *H. pylori* eradication. Further studies including metronidazole resistance and the efficacy of clarithromycin will be required.

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