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Influence of pretreatment with H2 receptor antagonists on the cure rates of *Helicobacter pylori* eradication

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: Pretreatment with a proton pump inhibitor (PPI) reportedly decreases the efficacy of *Helicobacter pylori* (*H. pylori*) eradication, however, the effect of pretreatment with an H2 receptor antagonist (H2RA) on *H. pylori* eradication has not yet been studied. We compared the efficacy of eradication regimen (lansoprazole/amoxicillin/clarithromycin) in patients with *H. pylori* infection with or without H2RA pretreatment.

Material/Methods: In this retrospective study conducted at three centers, 310 patients with *H. pylori* infection were treated. The diagnosis of *H. pylori* infection was made using the rapid urease test, bacterial cultures and histological examination of endoscopic biopsy specimens. The patients were assigned to receive an eradication regimen first or following pretreatment with H2RA. Eradication was assessed using the ^{13}C-urea breath test more than 4 weeks after the completion of therapy.

Results: Overall, *H. pylori* was eradicated in 79.7% of the cases: the eradication rate was 81.6% in the pretreatment group, and 77.6% in the eradication first group (p=0.3799, chi-square test). No significant difference in the eradication rate was observed between the two groups.

Conclusions: Pretreatment with H2RA had no significant influence on the efficacy of *H. pylori* eradication therapy.

key words: ***Helicobacter pylori*** **• eradication • proton pump inhibitor • H2 receptor antagonist • pretreatment**

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Background

In 1983, Barry J. Marshall and J. Robin Warren discovered *Helicobacter pylori* (*H. pylori*) in the gastric epithelium of patients with chronic active gastritis [1]. Infection with *H. pylori* plays a key role in the pathogenesis of a number of gastroduodenal and other diseases [2–9]. Colonization of the gastric mucosa with *H. pylori* results in the development of chronic gastritis in all infected individuals, and in a subset of patients, the chronic gastritis progresses further to peptic ulcer disease, gastric neoplasms, and other specific extragastric disorders. Colonization of the stomach with *H. pylori* is found in about half of the human population worldwide [2]. Therefore, effective *H. pylori* eradication is of enormous consequence.

There is general agreement that *H. pylori* should be eradicated in patients with peptic ulcers [6], but no consensus exists as to the optimal regimen [10–16]. In the Maastricht III Consensus Report, triple therapy using a PPI with clarithromycin and amoxicillin or metronidazole administered twice daily was the recommended treatment of first choice [17].

Several factors such as smoking, age, antibiotic resistance, short duration of therapy, poor compliance and genetic polymorphism of CYP2C19 have been shown to influence the eradication rate of *H. pylori* after appropriate therapy [9–15,17]. Another factor that has been implicated in the failure of therapy is pretreatment with antisecretory drugs, especially proton pump inhibitors (PPIs) [13–15,18–25]. Some data suggest that pretreatment with a PPI before the administration of *H. pylori* eradication therapy might decrease the efficacy of the treatment [13–15]. However, a meta-analysis investigating the influence of PPI pretreatment on triple and quadruple therapies for *H. pylori* eradication did not reveal any differences in the eradication rates between patients with and without pretreatment [25]. Thus, the issue of the influence of PPI pretreatment remains controversial. On the other hand, the effect of pretreatment with an H2 receptor antagonist (H2RA), which is capable of suppressing acid secretion to a similar degree as PPIs, on the efficacy rate of *H. pylori* eradication therapy has not yet been investigated. This issue has important practical implications, because patients are often already receiving antisecretory therapy when they are diagnosed as having *H. pylori* infection, and it would be useful to ascertain whether such therapy should be withdrawn prior to the start of the eradication therapy.

Material and Methods

Patients

We enrolled 310 consecutive outpatients (19–87 years old) who underwent upper gastrointestinal endoscopy at Yokohama City University Hospital, Yokohama Minami Kyosai Hospital or Fujisawa Shounandai Hospital between August 1998 and December 2007. All the enrolled patients were *H. pylori*-positive. The diagnosis of *H. pylori* infection was made using the rapid urease test, bacterial cultures and histological examination of endoscopic biopsy specimens. Complete information about the patients, including the age, sex, and smoking habit at the time of the initial diagnosis, was obtained from the patients' medical records. Patients with the "Smoking habit" in this study referred to those who were current regular smokers.

Table 1. Clinical characteristics of the patients enrolled in the present study.

Clinical characteristics		Number (%)
Total patients		310
Patient profiles		
Age	Median: range (in years)	54.7: 19–87
Sex	Female (%)/male (%)	100 (32.3)/ 210 (67.7)
Smoking habit	Smoker (%)/non-smoker (%)	105 (42.2)/ 144 (57.8)
Endoscopic results	Gastric ulcer (%)	101 (32.6)
	Duodenal ulcer (%)	98 (31.6)
	Gastroduodenal ulcer (%)	26 (8.4)
	Others (%)	85 (27.4)
Pretreatment	H2RA (%)	158 (51.0)
Duration of H2RA pretreatment: median (range) (in weeks)		10 (1–150)
Eradication data		
Medication duration: 1 week (%)/2 weeks (%)		305 (98.4)/5 (1.6)
Dosage of LPZ	30 mg (%)/60 mg (%)	5 (1.7)/291 (98.3)
Dosage of CAM	400 mg (%)/800 mg (%)	53 (17.9)/243 (82.1)
Eradication rate (%)		247/310 (79.7)

H2RA – H2 receptor antagonist; LPZ – lansoprazole; CAM – clarithromycin.

Exclusion criteria

Patients were excluded if they were receiving continuous treatment with NSAIDs or if they were pregnant or breast-feeding. Other exclusion criteria included poor compliance, known penicillin allergy, previous eradication therapy, previous treatment with PPIs, concomitant liver or kidney disease, severe cardiac or pulmonary disease, suspected or known malignancy, and the presence of Zollinger-Ellison syndrome or antral G cell hyperfunction.

Study design

In this retrospective study conducted at three centers, a total of 310 patients with *H. pylori* infection were treated. The patients were assigned to receive an eradication regimen (lansoprazole, clarithromycin, and amoxicillin) with or without pretreatment with an H2RA (famotidine, 20 mg or 40 mg, ranitidine, 150 mg or 300 mg, or lafutidine, 10 mg or 20 mg). All the patients underwent a ^{13}C-urea breath test (^{13}C-UBT) at least 4 weeks after the completion of the eradication therapy.

Table 2. Clinical characteristics of the patients according to the treatment group.

		Treatment groups		*P*-value
		H2RA pretreatment(+) group	H2RA pretreatment (–) group	
		(n=158)	(n=152)	
		Number (%)	Number (%)	
Age	Median: range (in years)	54: 20–87	56.5: 19–81	0.8121
Sex	Female (%)	47 (29.7)	53 (34.9)	0.3349*
Smoking habit	Current smoking (%)	60 (50.0)	45 (34.9)	0.0158*
Endoscopic results	Gastric ulcer (%)	63 (39.9)	38 (25.0)	
	Duodenal ulcer (%)	57 (36.1)	41 (27.0)	
	Gastroduodenal ulcer (%)	14 (8.9)	12 (7.9)	
	Others (%)	24 (15.2)	61 (40.1)	<0.0001**
Eradication therapy	Duration: 1 week (%)	156 (98.7)	149 (98.0)	0.6795***
	Dosage of LPZ: 60 mg (%)	148 (98.7)	143 (97.9)	0.6812***
	Dosage of CAM: 800 mg (%)	112 (74.7)	131 (89.7)	0.0007*
Eradication rate (%)		129 (81.6)	118 (77.6)	0.3799*

H2RA – H2 receptor antagonist; LPZ – lansoprazole; CAM – clarithromycin. P value: Mann-Whitney's *U* test; * Chi square test; ** 2×4 Chi square test; *** Fisher's exact test.

Eradication

H. pylori eradication therapy was administered using the standard 7-day or 14-day PPI-based triple therapy protocol (LPZ, 30 or 60 mg b.i.d. + amoxicillin, 1500 mg b.i.d. + clarithromycin [CAM], 400 or 800 mg b.i.d.) after obtaining informed consent from the patients. The possible adverse effects of the drugs were explained to the patients, who were encouraged to complete the treatment course.

All the patients underwent a ^{13}C-UBT at 4 weeks after the completion of the eradication therapy to confirm the eradication status of *H. pylori*. ^{13}C in excess of the cutoff value of 2.5% was considered to indicate active *H. pylori* infection, that is, failure of treatment.

Statistical analysis

For the statistical analysis, a chi-square test or Fisher's exact test was used to compare the percentages and Mann-Whitney's U test was used to compare continuous data. Various risk factors were also evaluated simultaneously using multiple logistic regression. In all tests, $p<0.05$ was regarded as indicative of statistical significance. The statistical analyses were performed using the Stat View software (SAS Institute, Cary, N.C.).

Ethics

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ethics Committee of Yokohama City University Hospital.

Results

The baseline characteristics of the study population are summarized in Table 1. A total of 310 cases (210 men and 100 women; median age, 54.7 years; range, 19–87 years) were enrolled in this study. The overall *H. pylori* eradication rate was 79.7%. Of the 158 patients who received H2RA pretreatment, 129 (81.6%) were cured, while 118 (77.6%) of the 152 patients who did not receive H2RA pretreatment were also cured (P=0.3799) (Table 2). No significant differences in the age, sex, smoking habit, endoscopic results, duration of eradication treatment, dosage of LPZ, dosage of CAM, percentage receiving pretreatment with H2RA, or duration of pretreatment with H2RA were noted between the two outcome groups (Table 3). Table 4 shows the results of the multivariate modeling. No significant difference in the outcome of eradication therapy was observed between the patients with and without H2RA pretreatment.

Discussion

Determining whether the timing of administration of antisecretory agents, such as PPIs and H2RAs, might have any influence on the efficacy rate of antibiotic treatment in patients with *H. pylori* infection is of clinical importance, because most patients with peptic ulcers have been treated with antisecretory agents prior to the initiation of *H. pylori* eradication treatment. The aim of this study was to investigate the influence of pretreatment with H2RA on the efficacy of *H. pylori* eradication therapy. Our results indicated that pretreatment with H2RA does not influence the efficacy of *H. pylori* eradication therapy.

Table 3. Clinical characteristics of the patients according to the success or failure of eradication therapy.

		Eradication		*P*-value
		Success (n=247)	Failure (n=63)	
		Number (%)	Number (%)	
Age	Median: range (in years)	55: 20–83	54: 19–87	0.7131
Sex	Female (%)	81 (26.1)	19 (30.2)	0.6896*
Smoking habit	Smoking (%)	82 (41.8)	23 (43.4)	0.8384*
Endoscopic results	Gastric ulcer (%)	78 (31.6)	23 (36.5)	
	Duodenal ulcer (%)	78 (31.6)	20 (31.7)	
	Gastroduodenal ulcer (%)	21 (8.5)	5 (7.9)	
	Others (%)	70 (28.3)	15 (23.8)	0.8567**
Eradication therapy	Duration: 1 week (%)	242 (98.0)	63 (100.0)	0.5631***
	Dosage of LPZ: 60 mg (%)	229 (97.9)	62 (100.0)	0.5441***
	Dosage of CAM: 800 mg (%)	193 (82.5)	50 (80.6)	0.7397*
	Pretreatment with H2RA (%)	129 (52.2)	29 (46.0)	0.3799*
Duration of H2RA pretreatment, median: range (in weeks)		20: 1-150	21: 1-100	0.4175

LPZ – lansoprazole; CAM – clarithromycin; H2RA – H2 receptor antagonist; P value: Mann-Whitney's *U* test; * Chi square test; ** 2×4 Chi square test; *** Fisher's exact test.

Table 4. Multiple logistic regression analysis to identify clinical factors associated with the success of eradication therapy.

Clinical factors	Odds ratio	95% confidence interval	*P*-value
Age	1.006	0.985–1.028	0.5759
Sex: Male	0.952	0.469–1.933	0.8913
Smoking habit	1.055	0.535–2.080	0.8768
Dosage of CAM: 800 mg	1.313	0.556–3.102	0.5339
H2RA pretreatment	1.146	0.610–2.150	0.6718

CAM – clarithromycin; H2RA – H2 receptor antagonist; R^2=0.003.

eradication therapy only for patients with gastroduodenal ulcer, gastric cancer after endoscopic therapy, gastric MALT lymphoma, and ITP with *H. pylori* positivity are covered by insurance in Japan now. In this study, the majority of patients had received eradication therapy for the prevention of recurrence of peptic ulcer.

Several studies have reported that pretreatment with antisecretory drugs was correlated with the failure of dual therapy with PPI and amoxicillin, with eradication rates being 30–70% lower among patients who had received PPI pretreatment [13–15]. Labenz et al. [13,14] reported that pretreatment with PPI resulted in a marked reduction in the *H. pylori* eradication rate. They speculated that treatment with a PPI directly or indirectly induced coccoid-persistent forms of *H. pylori*, resulting in lower cure rates. The coccoid-persistent form of *H. pylori* is known to be less vulnerable to the actions of antibiotics [26,27].

On the other hand, Adachi et al. [24] reported that pretreatment with omeprazole might actually improve the eradication rate (although there was no statistically significant difference). The strong antisecretory activity of PPIs has been thought to play an important role in the eradication of *H. pylori*, as PPI-induced high gastric pH has been reported to increase the sensitivity of *H. pylori* to antimicrobial agents [24,28–32]. Therefore, pretreatment with PPI or H2RA has been advocated based on the assumption that elevation of the gastric pH prior to the start of antibiotic administration would increase the cure rate [31,32]. While this issue concerning pretreatment with PPIs has remained controversial, a meta-analysis investigating the influence of PPI pretreatment on the efficacy of triple and quadruple *H. pylori* eradication therapies did not reveal any difference in the eradication rates between patients with and without PPI pretreatment [25]. This finding is of great practical importance when the immediate start of triple therapy is not possible, especially in cases where the antibiotic resistance must first be tested [32].

Since H2RAs also have strong antisecretory activity, pretreatment with H2RAs may improve the efficacy rate of *H. pylori* eradication therapy. However, PPIs not only directly block the proton pump on the parietal cells of the stomach, they have also been demonstrated, both *in vivo* and *in vitro*, to exhibit antibacterial activity against *H. pylori*. In contrast, H2RAs have no intrinsic antibacterial activity. Nevertheless, most studies comparing PPIs and H2RAs for *H. pylori* eradication

have not shown any significant differences between regimens including either drug. Consequently, the adjuvant effect of antisecretory therapy is related more to the drugs' ability to suppress acid secretion than to its antibacterial activity [33]. Because H2RAs have sufficient antisecretory effect for pretreatment, we hypothesized that H2RAs might be suitable for pretreatment and examined the influence of H2RA pretreatment on the efficacy rates of *H. pylori* eradication therapy. Moreover, even if H2RAs do not influence the form of existence of *H. pylori*, H2RA pretreatment might facilitate the eradication efficacy of triple/quadruple therapy against *H. pylori*. However, no significant difference in the efficacy of eradication therapy was observed between patients with and without H2RA pretreatment.

The findings of this retrospective study indicated that pretreatment with H2RA does not significantly reduce the efficacy of eradication therapy in patients with *H. pylori* infection. Further prospective cohort studies are needed to confirm this finding.

In the present study, other factors such as the age and smoking habit, which have been reported to influence the eradication rates of *H. pylori* in previous reports [14,34,35], were not found by multivariate logistic regression analysis to have any significant impact on the success rate of *H. pylori* eradication therapy (Table 4). One possible reason for this discrepancy is that clarithromycin resistance, which increases the risk of eradication failure [36–38], was not investigated in the present study.

During continuous treatment with a proton pump inhibitor (PPI), presence of significant nocturnal gastric acid secretion was reported [39]. This event, known as nocturnal gastric acid breakthrough (NAB), is defined as intragastric pH <4 for more than one hour continuously at night. Addition of an H2-receptor antagonist (H2RA) at bedtime to a high-dose PPI is likely to improve the nocturnal gastric pH control and decrease nocturnal gastric acid breakthrough [40]. The intragastric pH during *H. pylori* eradication treatment has been shown to affect the eradication rates [41]. Therefore, a PPI-based regimen with H2RAs at bedtime may improve the eradication rate of *H. pylori*, despite of contrary opinions [42].

And it was reported that use of H2RAs during and after *H. pylori* eradication therapy may be effective for preventing the occurrence of reflux esophagitis, gastric erosions and duodenal erosions after *H. pylori* eradication [43].

Conclusions

In summary, this retrospective study indicated that pretreatment with H2RA does not significantly influence the efficacy of eradication therapy in patients with *H. pylori* infection. Further prospective cohort studies are needed to confirm this finding from the perspectives of economic benefit and quality of life.

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