

Original Article



Pharmacodynamic evaluation of YH4808 for *Helicobacter pylori* eradication in healthy subjects

Hyeonsoo Park ^{1,2}, Choon Ok Kim ¹, Mikyung Kim ³, Yeji Lim ³,
Woo Yul Lee ^{1,2}, Sukyong Yoon ^{1,2}, and Min Soo Park ^{1,4,*}

¹Department of Clinical Pharmacology, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, Korea

²Department of Pharmacology, Yonsei University College of Medicine, Seoul 03722, Korea

³Clinical Development Department, R&D Division, Yuhan Corporation, Seoul 03722, Korea

⁴Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea



Received: Aug 19, 2020

Revised: Sep 16, 2020

Accepted: Sep 20, 2020

*Correspondence to

Min Soo Park

Department of Clinical Pharmacology,
Severance Hospital, Yonsei University College
of Medicine, Department of Pediatrics, Yonsei
University College of Medicine, 50-1 Yonsei-ro,
Seodaemun-gu, Seoul 03722, Korea.
E-mail: minspark@yuhs.ac

Copyright © 2020 Translational and Clinical
Pharmacology

It is identical to the Creative Commons
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>).

ORCID iDs

Hyeonsoo Park

<https://orcid.org/0000-0002-1133-8360>

Choon Ok Kim

<https://orcid.org/0000-0002-2319-1108>

Mikyung Kim

<https://orcid.org/0000-0002-4392-7864>

Yeji Lim

<https://orcid.org/0000-0001-7143-4656>

Woo Yul Lee

<https://orcid.org/0000-0003-3692-3491>

Sukyong Yoon

<https://orcid.org/0000-0002-9343-0901>

Min Soo Park

<https://orcid.org/0000-0002-4395-9938>

Trial Registration

ClinicalTrials.gov Identifier: NCT01921647

ABSTRACT

YH4808 is a novel selective potassium-competitive acid blocker demonstrated to be safe and to have inhibitory effects against gastric acid secretion in previous studies. A randomized, open-label, multiple-dose, 3-treatment, 1-period, parallel design study was conducted to compare the *Helicobacter pylori* eradication rates and acid suppression capacities of three regimens in 60 healthy subjects with *H. pylori*-positive, and the potential of YH4808 to replace proton-pump inhibitors (PPIs) in standard regimens for *H. pylori* eradication. Group 1 received YH4808, amoxicillin, and clarithromycin as a novel triple regimen, while Group 2 received YH4808 and amoxicillin only, and Group 3 received esomeprazole, amoxicillin, and clarithromycin, as the standard triple regimen. *H. pylori* eradication rates were 85.0% for Group 1, 25.0% for Group 2, and 83.3% for Group 3. Relative response rate between Group 1 and 3 was 1.02 (0.50–2.07; 95% CI, χ^2 test $p = 0.8881$). Furthermore, the novel triple regimen, YH4808, amoxicillin, and clarithromycin, stably inhibited acid secretion and maintained a gastric pH greater than 4 or 5 for 24 hours, which was comparable to the pH range in the standard triple regimen. However, the onset times of the YH4808 regimens were earlier than that for the regimens using esomeprazole. There were no differences in the incidences or severity of adverse events among the three groups. Overall, the novel triple regimen was safe and well-tolerated. YH4808 could replace PPIs in standard triple regimens used for *H. pylori* eradication.

Trial Registration: ClinicalTrials.gov Identifier: NCT01921647

Keywords: YH4808; *H. pylori*; Esomeprazole; Pharmacodynamics

INTRODUCTION

Helicobacter pylori is a bacterium parasite found in the mucous layer of the stomach. It secretes urease, which breaks down urea into ammonia to establish an environment conducive for its survival in the stomach [1]. *H. pylori* infection is a risk factor for various stomach diseases such as gastritis, gastric ulcers, duodenal ulcers, gastric cancer, and gastrointestinal cancer

Funding

This article was funded by Yuhan Corp, Seoul, Republic of Korea.

Reviewer

This article was reviewed by peer experts who are not TCP editors.

Conflict of Interest

- Authors: Yeji Lim and Mikyung Kim are employees of Yuhan Corp, The authors did not play any major roles in the study design and data analysis.
- Reviewers: Nothing to declare
- Editors: Nothing to declare

Authors Contributions

Conceptualization: Lim Y, Kim M; Data curation: Oh ES, Kim CO, Park MS; Formal analysis: Park H, Oh ES, Kim Y, Park MS; Methodology: Oh ES, Kim CO, Lim Y, Kim M, Park MS; Project administration: Oh ES, Kim CO, Park MS; Writing - original draft: Park H, Park MS; Writing - review & editing: Park H, Kim CO, Lee WY, Yoon S, Park MS.

[2]. Physicians recommend *H. pylori* eradication for certain conditions such as atrophic gastritis, stomach ulcers, early stomach cancer, and low-grade MALToma [3]. If a patient suffering from gastric ulcers undergoes *H. pylori* eradication therapy, the gastric ulcer recurrence rate is reduced to 5% [4]. The first-line treatment for *H. pylori* is a triple regimen including a proton-pump inhibitor (PPI), clarithromycin, and amoxicillin, with an eradication rate of approximately 80% [5,6].

PPIs prescribed with antibiotics enhance antibacterial activity by increasing stomach pH and stabilizing antibiotics, which could be degraded by acidic conditions in the stomach. PPIs such as esomeprazole inhibit H^+ and K^+ -ATPase by covalently binding to cysteines near ion-pathways. In addition, maintaining gastric pH above 4 or 5 enhances the antibacterial effects in *H. pylori* eradication therapies [7,8]. However, since PPIs are pro-drug forms of weak bases with pK_a in the 3.8–4.9, they must be accumulated in the luminal surface of the stomach, where the pH is about 1.0, and transformed into activated forms [9]. Such modes of administration could have contrasting effects on different antibiotics. For example, amoxicillin and clarithromycin are unstable at $pH < 2$ in the stomach, while clarithromycin is likely to be degraded [10]. Similarly, the effects of the antibiotics can be slow before meals. Conversely, YH4808, developed by Yuhan Corporation, is a selective K^+ competitive acid blocker (P-CAB), which competitively inhibits the proton pump through the potassium-dependent pathway. Since it is not a pro-drug, it does not require gastric acid activation; therefore, the onset of action is rapid so that it is effective. In addition, the polymorphism of the *CYP2C19* genotype influences the *H. pylori* eradication rate of esomeprazole-based triple therapy. The eradication rate of *H. pylori* was significantly lower in EM than in non-EM [11,12]. However, the pharmacodynamic response of YH4808 is not highly affected by the *CYP2C19* genotype [13].

In a previous study comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of YH4808 and esomeprazole administered for 7 days to healthy subjects, YH4808 was superior to esomeprazole with regard to 24-hour gastric acid secretion inhibition and night acid secretion inhibition, in addition to tolerability and safety. In addition, the mean gastric pH over 24 hours was greater than 5 for YH4808, when compared with 4.3 for esomeprazole. In addition, the increasing pH after dosing seemed more rapid under YH4808 than under a PPI [13]. The results suggest that YH4808 could be used in place of PPIs in standard triple regimen for *H. pylori* eradication.

The PK drug interactions among YH4808, clarithromycin, and amoxicillin have been previously studied [14]. The aim of the present study was to evaluate and compare the PD responses of a potential novel triple or double treatment regimen for *H. pylori* eradication, which replaces esomeprazole with YH4808, with a standard triple regimen using esomeprazole.

METHODS

Study participants and design

The study was conducted at the clinical trials center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. The study was registered in The ClinicalTrial.gov. (Registration number: NCT01921647). Healthy Korean volunteers aged 20–55 years, weighing 55 kg or more, with a body mass index between 18.5 and 25.0 kg/m^2 and who tested positive for *H. pylori* in a ^{13}C -Urea breath test were enrolled in the present study. All participants provided written informed consent before being admitted into the study.

The health of subjects was screened based on medical history, physical examination, a 12-lead electrocardiogram (ECG), vital signs, and laboratory tests.

Subjects with a potential history of allergic reaction to YH4808, esomeprazole magnesium, amoxicillin, and clarithromycin, or significant gastrointestinal disease, or history of major surgery were excluded. Heavy smokers (more than 10 cigarettes a day), habitual drinkers, and those who consume excessive caffeine were ineligible. Consumption of foods and beverages containing caffeine, alcohol, and grapefruit juice, as well as prescription drugs or oriental herbal medicines that could potentially interact with YH4808 was prohibited in the course of the study.

This study was a randomized, open-label, multiple-dose, 3-treatment, 1-period, parallel design study. Sixty healthy subjects were enrolled and randomly assigned to 3 groups, with 20 subjects per group. Group 1 (YH+A+C) took 200 mg of YH4808 (Yuhan Corporation, Seoul, Korea), 1,000 mg of amoxicillin (Dongwha Pharm Corporation, Seoul, Korea), and 500 mg of clarithromycin (Abbott Korea Limited, Seoul, Korea) 30 minutes after meals BID for 7 days. Group 2 (YH+A) took 200 mg of YH4808 and 1,000 mg of amoxicillin 30 minutes after meals for 7 days, while Group 3 (N+A+C) took 20 mg of esomeprazole (Astrazeneca, Seoul, Korea), 100 mg of amoxicillin, and 500 mg of clarithromycin 1 hour before meals BID for 7 days.

H. pylori eradication rate and 24-hour pH monitoring

At least 14 days after the last dose of the 7-day administration, the ¹³C-urea breath test for *H. pylori* was performed again to evaluate the antibacterial effects of the three *H. pylori* eradication regimens adopted. The ¹³C-urea breath test yields high sensitivity and specificity for diagnosis of *H. pylori* infections [15].

Ambulatory 24-hour pH recording (Gastroesophageal reflux monitoring: pH and impedance Radu Tutuian and Donald O. Castell GI Motility online, 2006) was used to measure gastric pH continuously. A pH electrode was inserted into the stomach through the nasal cavity, and the lower end of the probe placed 5 cm below the lower end of the esophagus to measure pH with a constant time interval. The total pH measurement time was 1440 minutes (24 hours), and each measurement was obtained automatically every 5 seconds. The mean pH, which represented the averages of the measured for 1 minute, were obtained using the moving average method. In addition, to minimize variability through potential effects of posture on gastric pH, the subjects were instructed to maintain a supine position at bedtime from 11:00 PM up to the following morning at 7:00 AM, and to maintain an upright position of 45 degrees or greater from 7:00 AM to 11:00 PM.

Pharmacodynamic analysis

In the present study, PD analysis was conducted for the participants who took the medication and completed the gastric pH monitoring for 24 hours (7:00 AM on Day 1–7:00 AM on Day 2, 7:00 AM on Day 7–7:00 AM on Day 8). As exploratory efficacy biomarker, the number and proportion of subjects with a negative ¹³C-urea breath test during the post-study visit were analyzed. The arithmetic mean and median of the gastric pH for 24 hours, the duration and proportion over which gastric pH was maintained at ≥ 4 or ≥ 5 for 24 hours were analyzed as PD parameters. Also, The areas under the effect curves (AUECs) for pH*time from 0 to 2 hours and from 0 to 4 hours as well as pH*time from 0 to 24 hours were analyzed to evaluate early effect of the PPIs. The antibacterial effects of the three treatment groups were compared and evaluated based on the parameters defined above.

Safety assessment

All subjects who had taken at least one dose of the prescribed medication were monitored for safety throughout the study. Adverse event monitoring, vital signs (temperature, blood pressure, pulse), laboratory tests (hematology, blood chemistry, and urinalysis), 12-lead ECG, and physical examination data were collected and evaluated as safety assessment parameters. Causality, frequency, and severity of adverse events were characterized based on the last dose for the different treatment groups.

Statistical analysis

All statistical analyses were conducted in SAS v9.2 (SAS Institute, Inc., Cary, NC, USA). The results of ^{13}C -urea breath test at least 14 days after the last dose and the number and proportion of *H. pylori* negative subjects, as the exploratory efficacy biomarker were evaluated for each treatment group, and the differences between groups were analyzed using the χ^2 test and the relative response rate (RR). In addition, the 24 hours gastric pH profiles were compared among treatment groups. Differences between Group 1 and Group 3, and Group 1 and Group 2, were tested using the independent t-test (inter-group difference of the pH change from Day 1 to 7) and the paired t-test (pH change from Day 1 to 7 in the same group). Further analyses were performed using the repeated Analysis of Variance as required. Differences in subject distribution were compared depending on whether the *H. pylori* was eradicated or not in each group.

Ethics approval

The present study was performed in compliance with the principles of the Declaration of Helsinki and Korean Good Clinical Practice regulations. The protocol was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2013-0311).

RESULTS

Study subjects

In total, 60 healthy men age 23–52 years (32.2 ± 6.7 years) with a body mass index of 18.6–24.9 kg/m^2 ($22.6 \pm 1.8 \text{ kg}/\text{m}^2$) were enrolled (**Table 1**); 2 subjects withdrew prior to dosing and were replaced. In the course of the study, 2 subjects dropped out and the remaining 58 subjects completed the study. In addition, only pH data from 57 participants were analyzed because pH values were all negative over 24 hours due to an unknown technical error. Negative pH values in the test subjects were excluded from the pH data analyses as they were considered to be noise or artifacts, temporary poor signals from the device, or were deemed not physiologically practical. The disposition of subjects is summarized in **Fig. 1**.

Table 1. Demographic characteristics of subjects

Demographic variables	Treatment (mean \pm standard deviation)			Total (n = 60)	p-value*
	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)		
Age (yr)	32.9 \pm 7.2	32.5 \pm 6.7	31.3 \pm 6.4	32.2 \pm 6.7	0.782
Weight (kg)	71.6 \pm 7.0	70.5 \pm 7.2	65.8 \pm 7.0	69.3 \pm 7.4	0.033
Height (cm)	177.0 \pm 5.1	175.3 \pm 4.8	172.5 \pm 4.7	174.9 \pm 5.1	0.022
BMI (kg/m^2)	22.8 \pm 1.5	22.9 \pm 1.9	22.0 \pm 2.0	22.6 \pm 1.8	0.284
Smoking (yes/no)	5/15	8/12	6/14	19/41	0.692
Drinking (yes/no)	5/15	9/11	4/16	18/42	0.289
Caffeine (yes/no)	9/11	10/10	9/11	28/32	1.000

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID for 7 days; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days.

BMI, body mass index.

*p-value for Fisher's exact Test, Kruskal-Wallis Test.

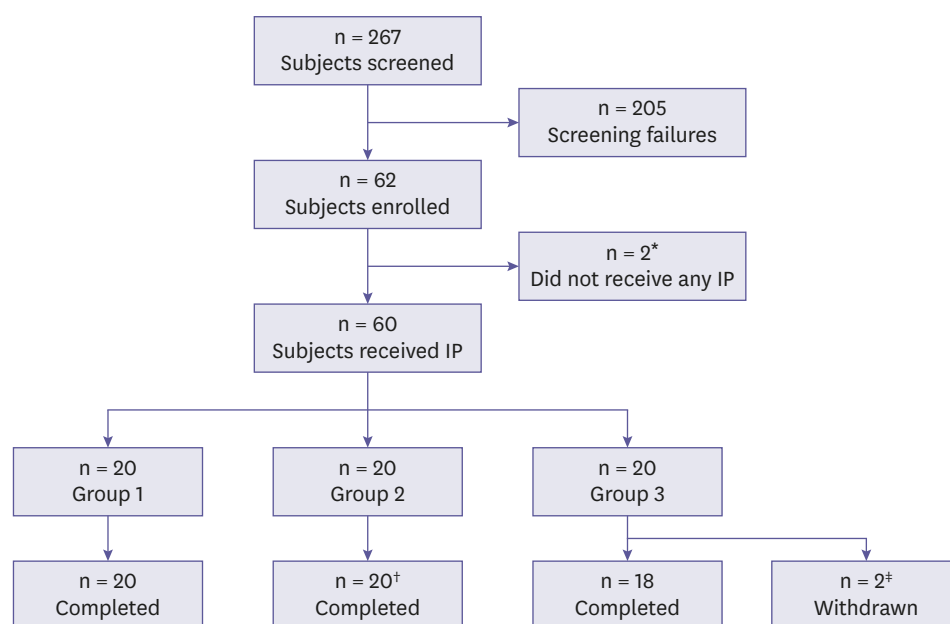


Figure 1. Disposition of subjects.

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID for 7 days; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days.

IP, investigational products.

*Subjects requested withdrawal of consent; †A subject's pH value was excluded from the intra-gastric pH evaluation due to an unknown technical error, but the subject's result of ^{13}C -Urea Breath test was included in the eradication rate evaluation; *Subjects dropped out due to study protocol deviation.

Exploratory efficacy analysis

The results of the ^{13}C -Urea Breath test conducted at least 14 days after the last repeated dose were as follows. After 7 d of repeated administration of the triple or double *H. pylori* regimens, the eradication rates of Group 1, Group 2, and Group 3 were 85.0%, 25.0%, and 83.3%, respectively (**Fig. 2**). The eradication rate of the Group 1 was 1.7% greater than that of the Group 2 with an RR (95% CI) of 1.02 (0.50–2.07); (95% CI, χ^2 test $p = 0.8881$). The eradication rate was significantly higher in Group 1 than in Group 2 with an RR (95% CI) of 3.40 (1.25–9.22);

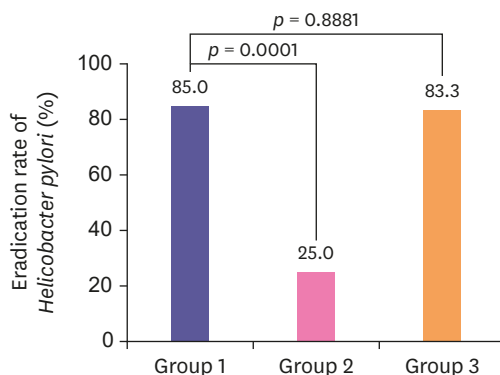


Figure 2. *H. pylori* eradication results.

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg (Group 3) BID. Group 1 vs. Group 2; Group 1 vs. Group 3. The p -values obtained are based on the χ^2 test.

Table 2. ¹³C-Urea breath test results after *H. pylori* treatment regimens

Groups	Negative	Positive	Negative/Total	RR (95% CI)*
Group 1 (n = 20)	17	3	0.85	-
Group 2 (n = 20)	5	15	0.25	3.40 (1.25–9.22)
Group 3 (n = 18)	15	3	0.833	1.02 (0.50–2.07)

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID for 7 days; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days.

RR, relative response rate.

*Relative response rate of 2 groups; Group 1 as a reference.

(95% CI, χ^2 test, p -value = 0.0001). In addition, the eradication rate of Group 3 was significantly higher than that in Group 2 (χ^2 test, p -value = 0.0010) (Table 2).

Pharmacodynamic analysis

The median values of intra-gastric pH vs. time profiles for 24 hours following the administration of *H. pylori* treatment regimen (Day 7 and Day 1) are plotted in Fig. 3 and the mean values of pH monitored during *H. pylori* treatment regimens between groups and within groups are summarized in Table 3. There were no significant differences in mean pH values between Group 1 and Group 3 at Day 1 and at Day 7 ($p = 0.2368$ and $p = 0.4138$, respectively). In addition, pH values in Group 1 and Group 3 did not change significantly between Day 1 and Day 7 ($p = 0.0629$). Conversely, there was a significant difference in the pH between Group 1 and Group 2 ($p = 0.0096$) value of Day 1, which was not observed at Day 7 ($p = 0.0593$). In addition, there was no significant difference in between Day 1 and Day 7 ($p = 0.0822$). Within each dose group, there was no significant difference in pH value between Day 1 and Day in Group 1 ($p = 0.1141$); however, there were significant differences in Group 2 and in Group 3 ($p = 0.0095$ and $p = 0.0011$ respectively).

The mean proportions of time over 24 hours period when pH was maintained ≥ 4 (%time pH ≥ 4) or ≥ 5 (%time pH ≥ 5) in the different treatment regimens on Day 1 and Day 7 were as follows. On Day 1, the %time pH ≥ 4 or %time pH ≥ 5 in the course of *H. pylori* treatment were 85.9% and 79.6% in Group 1, 72.9% and 65.1% in Group 2, and 77.6% and 71.3% in Group 3, respectively. On Day 7, the proportions were 95.2% and 87.7% in Group 1, 88.5% and 77.4% in Group 2, and 95.8% and 90.2% in Group 3, respectively. The %time pH ≥ 4 or pH ≥ 5 between

Table 3. Summary of pharmacodynamic outcomes

Parameters	Treatments				
	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 18)	Group 1–Group 2*	Group 1–Group 3†
Mean pH‡					
D1	6.03 \pm 0.43	5.37 \pm 0.94	5.66 \pm 1.23	0.66 \pm 0.23§	0.37 \pm 0.29
D7	6.21 \pm 0.50	5.84 \pm 0.66	6.34 \pm 0.46	0.36 \pm 0.19	-0.13 \pm 0.16
D7–D1	0.17 \pm 0.11	0.47 \pm 0.12§	0.68 \pm 0.23§	-0.30 \pm 0.17	-0.50 \pm 0.25
Proportion of time (%)‡					
pH ≥ 4					
D1	85.9 \pm 6.3	72.9 \pm 17.9	77.6 \pm 5.2	13.0 \pm 4.2§	8.28 \pm 5.1
D7	95.2 \pm 8.4	88.5 \pm 12.0	95.8 \pm 7.4	6.7 \pm 3.3	-0.6 \pm 2.6
D7–D1	9.3 \pm 2.1§	15.6 \pm 2.7§	18.2 \pm 4.5§	-6.3 \pm 3.4	-8.9 \pm 4.8
pH ≥ 5					
D1	79.6 \pm 8.8	65.1 \pm 22.5	71.3 \pm 5.9	14.6 \pm 5.4§	8.3 \pm 6.0
D7	87.7 \pm 14.3	77.4 \pm 16.8	90.2 \pm 10.7	10.3 \pm 5.0§	-2.5 \pm 4.1
D7–D1	8.0 \pm 3.2§	12.3 \pm 3.5§	18.8 \pm 4.9§	-4.3 \pm 4.7	-10.8 \pm 5.7

* Δ pH of 2 groups, Group 2 as a reference; † Δ pH of 2 groups, Group 3 as a reference; ‡Plus-minus values are means \pm standard deviation in each group at Day 1 and Day 7, means \pm standard error in both inter/intra group comparisons; § p -value < 0.05 by independent or paired t-test

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID for 7 days; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days.

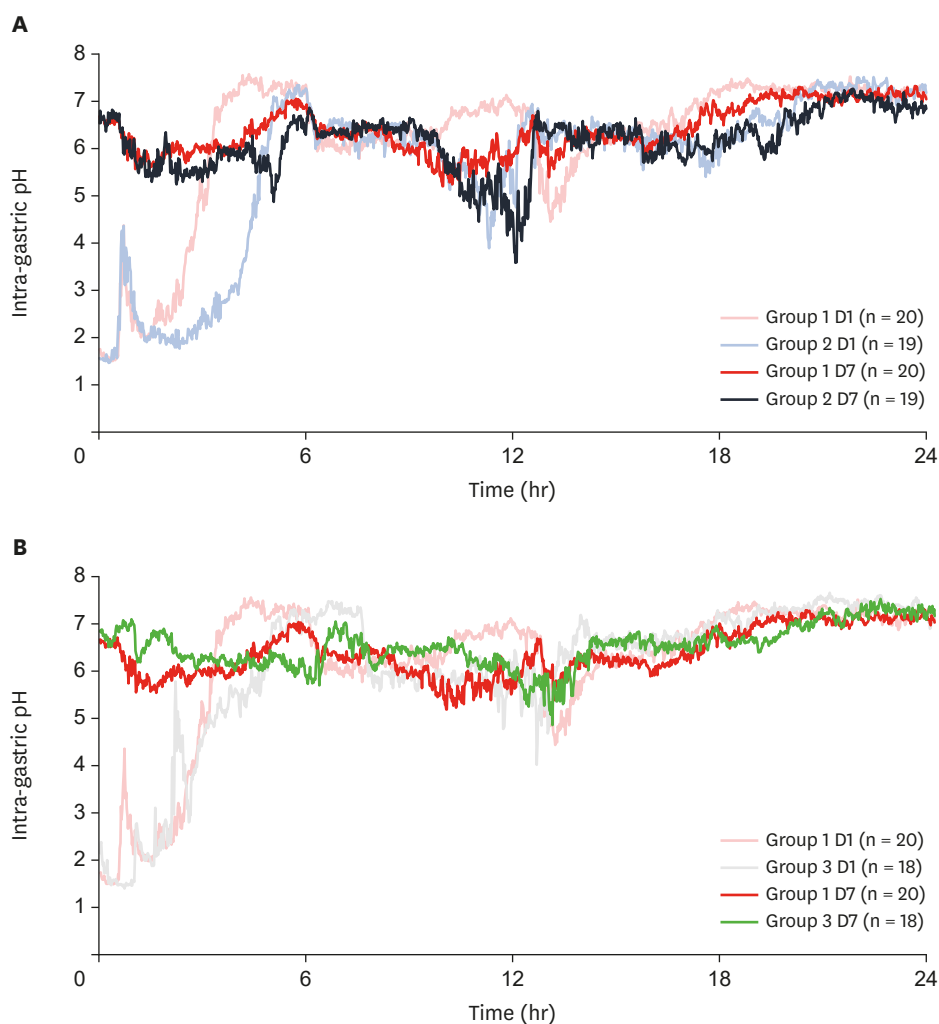


Figure 3. Median 24-hour intra-gastric pH vs. time profiles following *H. pylori* treatment regimen administration. D1, 7:00 AM on Day 1–7:00 AM on Day 2; D7, 7:00 AM on Day 7–7:00 AM on Day 8. (A) YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID (Group 1) vs. YH4808 200 mg + Amoxicillin 1,000 mg BID (Group 2); (B) YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg (Group 1) BID vs. Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg (Group 3) BID.

the Group 1 and Group 2 was significantly different on Day 1 and on Day 7. However, there were no significant differences between Group 1 and Group 3 (Table 3).

The areas under the effect curve (AUECs) (pH*min) following oral administration of *H. pylori* treatment regimens are summarized in Table 4. The AUEC for pH-time was calculated (0 to 2, 4, and 24 hours post-dose) to evaluate the starting point at which pH increased. AUEC (0–24 hours) and AUEC (0–4 hours) on Day 1 in Group 1 were larger than that in Group 2. On Day 7, AUEC (0–4 hours) in Group 2 was as large as 94.5 pH*min, which was significantly larger than that in Group 1; however, there was no significant difference in AUEC (0–24 hours) among all the treatment regimens on Day 7.

Safety

Sixty participants were included in the safety assessment. Adverse events occurred in 22 subjects (36.7%, 32 cases) in the present study. All the adverse events were mild and none were severe. The group with the highest incidence of adverse events was Group 3 (8 subjects,

Table 4. Area under the effect curve (pH*min) following oral administration of *H. pylori* treatment regimens (supplement)

Parameters	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 18)	Group 1–Group 2*	Group 1–Group 3†
AUEC (0–24 hr)‡					
D1	8,687.9 ± 612.1	7,736.2 ± 1,351.7	8,153.3 ± 1,768.8	951.7 ± 333.1§	534.6 ± 420.5
D7	8,938.3 ± 726.0	8,413.8 ± 948.0	9,125.5 ± 663.1	524.5 ± 269.5	–187.2 ± 226.5
D7–D1	250.4 ± 164.4	677.6 ± 173.9§	972.2 ± 332.5§	–427.2 ± 239.1	–721.8 ± 359.6
AUEC (0–2 hr)‡					
D1	327.2 ± 78.0	340.4 ± 125.6	361.1 ± 232.5	–13.2 ± 33.3	–33.8 ± 55.1
D7	710.4 ± 64.4	697.1 ± 98.7	769.2 ± 95.4	13.2 ± 26.6	–58.8 ± 26.2
D7–D1	383.1 ± 16.9§	356.7 ± 26.4§	408.1 ± 52.9§	26.4 ± 31.0	–25.0 ± 53.2
AUEC (0–4 hr)‡					
D1	916.8 ± 167.1	683.5 ± 220.1	875.4 ± 347.8	233.3 ± 62.4§	41.4 ± 87.1
D7	1,415.5 ± 121.7	1,347.9 ± 226.3	1,510.0 ± 106.4	67.7 ± 57.8	–94.5 ± 37.3§
D7–D1	498.7 ± 30.6§	664.3 ± 46.5§	634.6 ± 77.2	–165.6 ± 55.2§	–135.9 ± 79.9

Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID for 7 days; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID for 7 days.

*ΔAUEC of 2 groups, Group 2 as a reference; †ΔAUEC of 2 groups, Group 3 as a reference; ‡Plus-minus values are means ± standard deviation in each group on D1 and D7, means ± standard error in inter/intra group comparisons; §p-value < 0.05 by independent or paired t-test.

16 cases). There were 18 adverse events that were suspected to have a causal relation with the prescribed medication, including 5 subjects (6 cases) in Group 1 for YH4808, amoxicillin and clarithromycin, 6 subjects (6 cases) in Group 2 for YH4808 and amoxicillin and 4 subjects (6 cases) in Group 3 for esomeprazole, amoxicillin and clarithromycin, with no significant differences between the groups in the number of the subjects who had adverse events suspected to have a causal relationship with the treatment (Fisher's exact test: $p = 0.930$). There was a total of 11 cases associated with gastrointestinal disorder. Headache was the most frequently reported adverse event and all adverse events were mild in severity. There were no serious adverse events in the present study and no clinically relevant changes were observed in vital signs, physical examination, ECG, and clinical laboratory tests, including serum gastrin.

DISCUSSION

The objective of the present study was to explore the potential of replacing esomeprazole, which is widely used as part of the standard triple regimen in *H. pylori* eradication therapies, with YH4808. Since the acid inhibition effect of esomeprazole has been demonstrated, We conducted the study to compare pharmacodynamic parameters of the standard regimen and the novel regimens. We enrolled healthy subjects who were *H. pylori* positive based on the ¹³C-urea breath test and compared pharmacodynamic parameters and safety profiles among patients who received the standard triple regimen composed of esomeprazole, amoxicillin, and clarithromycin, a novel triple regimen using YH4808 in place of esomeprazole, and a novel double regimen consisting of YH4808 and amoxicillin.

Current clinical evidence suggests that PPIs (e.g., esomeprazole 40 mg QD or 20 mg BID), clarithromycin 500 mg BID, and amoxicillin 1,000 mg BID (or metronidazole 500 mg BID) administered for 14 days would achieve over 80% eradication, whereas the same regimen administered for 7 days achieves approximately 70% eradication [16,17]. In our studies, we used the same regimen for only 7 days, since the objective of the study was not to assess clinical efficacy of the treatments in patient populations but to compare short-term biomarkers between treatment regimens under similar conditions. The actual eradication rates were 85.0% (17 out of 20 subjects), 25.0% (5 out of 20 subjects), and 83.3% (15 out of 18 subjects) for the Group 1, Group 2, and Group 3, respectively. The eradication rates

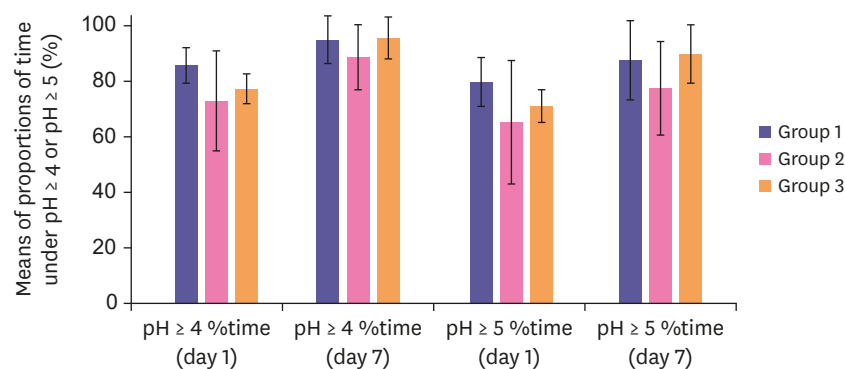


Figure 4. *H. pylori* treatment groups vs. Means of proportions of time under pH \geq 4 or pH \geq 5 (Day 7 and Day 1). Group 1, YH4808 200 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg BID; Group 2, YH4808 200 mg + Amoxicillin 1,000 mg BID; Group 3, Esomeprazole 20 mg + Amoxicillin 1,000 mg + Clarithromycin 500 mg (Group 3) BID.

of both triple regimens, Group 1 and Group 3, were much higher than expected based on literature, while there were no significant differences between the two regimens (95% CI of RR, 0.50–2.07). The double regimen did not yield a satisfactory response when compared with Group 1 or Group 3 (95% CI of RR, 1.25–9.22). We designed the novel double regimen with expecting a pharmacodynamic effect comparable to the triple regimens, but unfortunately, it did not.

Generally, the mean pH, %time pH \geq 4 or pH \geq 5 values were notably higher in Group 1 than in Group 3 on Day 1 but only a little lower or similar on Day 7. Although there were no significant differences between the two regimens on Days 1 and 7, it is notable that Group 1 exhibited a trend where high pH was achieved quite rapidly with only one day of administration when compared with Group 3 (Fig. 4). The finding is consistent with YH4808 properties, which is a selective K⁺ competitive acid blocker. In addition, it is not a pro-drug and does not require acid-driven activation, which is the case in numerous PPIs. Only the Group 1 did not exhibit significant difference in mean gastric pH for 24 hours between Day 1 and Day 7 (independent or paired t-test, *p*-value > 0.05); i.e., YH could effectively increase gastric pH rapidly and maintain it at the relatively high levels even on Day 1. Similarly, there was no difference in AUEC (0–24 hours) between Day 1 and Day 7. In other words, Group 1 regimen could increase gastric pH rapidly even on Day 1 to a level that could be achieved on Day 7, whereas the effect of the Group 3 regimen was not as rapid as that of Group 1

With regard to the safety profiles, adverse events, including gastrointestinal system-associated symptoms, the symptoms in the Group 1 were the fewest when compared to the other groups, although there were no significant differences. Previous studies have also demonstrated that Group 1 regimen can be taken regardless of mealtime, which minimizes the chances of treatment failure due to poor medication compliance by a patient [18].

In conclusion, the results of the present study demonstrate that a novel triple regimen that adopts a P-CAB, namely YH4808, as opposed to a PPI is as effective as the conventional standard triple treatment regimen of esomeprazole, amoxicillin, and clarithromycin. The *H. pylori* eradication rates between Group 1 and Group 3 were similar with no significant differences. In addition, YH4808 increased gastric pH relatively rapidly and maintained it almost as effectively as esomeprazole, if not better. Overall, YH4808 could replace PPIs in standard triple regimens used for *H. pylori* eradication.

ACKNOWLEDGEMENTS

We thank the staff at Severance Hospital Clinical Trials Center for their cooperation.

REFERENCES

1. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev* 2006;19:449-490.
[PUBMED](#) | [CROSSREF](#)
2. Blaser MJ. *Helicobacter pylori* and gastric diseases. *BMJ* 1998;316:1507-1510.
[PUBMED](#) | [CROSSREF](#)
3. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007;56:772-781.
[PUBMED](#) | [CROSSREF](#)
4. Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996;110:1244-1252.
[PUBMED](#) | [CROSSREF](#)
5. Heo J, Jeon SW. Changes in the eradication rate of conventional triple therapy for *Helicobacter pylori* infection in Korea. *Korean J Gastroenterol* 2014;63:141-145.
[PUBMED](#) | [CROSSREF](#)
6. Kim TH, Park JM, Cheung DY, Oh JH. Comparison of 7- and 14-day eradication therapy for *Helicobacter pylori* with first- and second-line regimen: randomized clinical trial. *J Korean Med Sci* 2020;35:e33.
[PUBMED](#) | [CROSSREF](#)
7. Ierardi E, Losurdo G, Fortezza RF, Principi M, Barone M, Leo AD. Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: old and new tricks to improve effectiveness. *World J Gastroenterol* 2019;25:5097-5104.
[PUBMED](#) | [CROSSREF](#)
8. Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, et al. Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. *Helicobacter* 2007;12:317-323.
[PUBMED](#) | [CROSSREF](#)
9. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep* 2008;10:528-534.
[PUBMED](#) | [CROSSREF](#)
10. Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori*. *Gastroenterology* 2007;133:985-1001.
[PUBMED](#) | [CROSSREF](#)
11. Saito Y, Serizawa H, Kato Y, Nakano M, Nakamura M, Saito H, et al. First-line eradication for *Helicobacter pylori*-positive by CYP2C19 genotype. *World J Gastroenterol* 2015;21:13548-13554.
[PUBMED](#) | [CROSSREF](#)
12. Kang JM, Kim N, Lee DH, Park YS, Kim JS, Chang JJ, et al. Effect of the CYP2C19 polymorphism on the eradication rate of *Helicobacter pylori* infection by 7-day triple therapy with regular proton pump inhibitor dosage. *J Gastroenterol Hepatol* 2008;23:1287-1291.
[PUBMED](#) | [CROSSREF](#)
13. Yi S, Lee H, Jang SB, Byun HM, Yoon SH, Cho JY, et al. A novel K⁺ competitive acid blocker, YH4808, sustains inhibition of gastric acid secretion with a faster onset than esomeprazole. *Aliment Pharmacol Ther* 2017;46:337-346.
[PUBMED](#) | [CROSSREF](#)
14. Lee WY, Oh E, Cui M, Kim CO, Lim Y, Kim H, et al. Evaluation of pharmacokinetic interactions between amoxicillin, clarithromycin, and the potassium-competitive acid blocker YH4808 in healthy subjects. *Transl Clin Pharmacol* 2020;28:55-65.
[PUBMED](#) | [CROSSREF](#)
15. Choi JM, Kim SG. Diagnosis and treatment of *Helicobacter pylori* infection: Korean and overseas guidelines. *Korean J Med* 2015;89:157-168.
[CROSSREF](#)
16. Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, et al. Optimum duration of regimens for *H. pylori* eradication. *Cochrane Database Syst Rev* 2013:CD008337.

17. Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for *Helicobacter pylori* eradication. *Ann Intern Med* 2007;147:553-562.
[PUBMED](#) | [CROSSREF](#)
18. Wermeille J, Cunningham M, Dederding JP, Girard L, Baumann R, Zelger G, et al. Failure of *Helicobacter pylori* eradication: is poor compliance the main cause? *Gastroenterol Clin Biol* 2002;26:216-219.
[PUBMED](#)