

## Original Article



# Evaluation of pharmacokinetic interactions between amoxicillin, clarithromycin, and the potassium-competitive acid blocker YH4808 in healthy subjects

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## ABSTRACT

YH4808 is a novel potassium-competitive acid blocker that was developed as a therapeutic agent for gastric acid-related diseases; it may replace proton pump inhibitors, which are widely used in combination with amoxicillin and clarithromycin for *Helicobacter pylori* eradication. We compared the pharmacokinetic (PK) profiles and safety of amoxicillin, clarithromycin, and YH4808 used as monotherapies or in combination for evaluating potential drug interactions. An open-label, randomized, single-dose, Latin-square (4 × 4) crossover study was conducted in 32 healthy Korean volunteers. Subjects were randomly assigned to one of the 4 treatment sequences that consisted of 4 periods separated by 21-day washout intervals. PK parameters of YH4808, amoxicillin and clarithromycin administered in combination were compared with those of the respective monotherapies. The geometric mean ratios of the maximum concentration ( $C_{max}$ ) and the area under the time-concentration curve from time zero to time of the last quantifiable concentration ( $AUC_{last}$ ) of YH4808 increased during the triple therapy by 48.6% and 29.1%, respectively. Similarly, the  $C_{max}$  and  $AUC_{last}$  of M3 (active metabolite of YH4808) increased by 23.3% and 16.0%, respectively. The  $C_{max}$  and  $AUC_{last}$  of clarithromycin increased by 27.4% and 30.5%, and those of 14-hydroxyclearithromycin were increased by 23.1% and 32.4%, respectively. The corresponding amoxicillin values decreased during the triple therapy by 21.5% and 15.6%, respectively. There was no clinically significant change in safety assessment related to either monotherapies or triple therapy. In conclusion, amoxicillin, clarithromycin and YH4808 administered as triple therapy did not exhibit significant PK interactions and were not associated with safety issues.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT01921647

**Keywords:** *Helicobacter pylori*; Triple therapy; Potassium-competitive acid blocker; Pharmacokinetics; Drug interactions

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**Reviewer**

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**Conflict of Interest**

- Authors: Yeji Lim and Hunam Kim are employees of Yuhan Corp. The authors have no other potential conflicts of interest to disclose regarding the content of this article.
- Reviewers: Nothing to declare
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**Author Contributions**

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

## INTRODUCTION

*Helicobacter pylori* is a gram-negative, microaerophilic bacillus that colonizes the mucus layer and the inner surface of the gastroduodenal epithelium, where it causes various gastrointestinal (GI) diseases, including chronic gastritis, peptic ulcer, and gastric cancer [1]. More than 90–95% of duodenal ulcer and 70–85% of gastric ulcer cases are associated with *H. pylori* infection [2], and there is a significant decrease in peptic ulcer relapse after successful *H. pylori* eradication [3].

Various drug combinations have been used to treat *H. pylori* infections, including the combination regimen of a standard dose of a proton pump inhibitor (PPI), 1,000 mg amoxicillin, and 500 mg clarithromycin, concurrently administered twice daily for 7 or 14 days as first-line therapy [4]. The PPIs, which play a critical role in eradicating *H. pylori*, has different clinical effects. It reduces the urease activity of *H. pylori* and inhibits the pathogen's growth by lowering gastric acid secretion [5]. The increase of the gastric pH by PPI stabilizes the co-administered antibiotics such as beta-lactam or macrolides, which generate a synergistic effect by enhancing the bactericidal activity of the antibiotics [6]. However, PPIs have a slow onset of action [7] and demonstrate inter-individual variability of drug exposure and response due to the genetic polymorphism of enzyme that metabolize them, such as cytochrome P450(CYP) 2C19 [8,9].

Potassium-competitive acid blockers (P-CABs) represent a novel acid suppressant class. They reversibly bind to the hydrogen potassium ATPase ( $H^+/K^+$ -ATPase) of gastric parietal cells and inhibit gastric acid secretion. YH4808, developed by Yuhan Corp. is a P-CAB with a faster onset time. Unlike a PPI, which depends on activation by gastric acid for generating a pharmacological effect, a P-CAB is not a prodrug and has direct effects. In an earlier first-in-human study, YH4808 exerted a rapid, sustained suppression of gastric acid secretion, compared to esomeprazole. Moreover, the pharmacokinetic (PK) and pharmacodynamics of YH4808 were not significantly affected by CYP2C19 polymorphism, which is known to interfere with PPI-based therapies [10]. YH4808 was considered a reasonable candidate to replace PPIs as a component of the triple therapy regimen for *H. pylori* eradication. YH4808 is metabolized by several hepatic enzymes such as CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 [11]. Clarithromycin and amoxicillin, being respectively an inhibitor of CYP3A4 and CYP2C8, there is a possibility of developing drug interactions when used as triple therapy [12,13]. In this study, to evaluate potential interactions between amoxicillin, clarithromycin, and YH4808 used in combination, we compared the PK profiles of these drugs administered as monotherapies or in combination as triple therapy.

## METHODS

### Ethics

This study was conducted at the Clinical Trials Center, Severance Hospital, Yonsei University College of Medicine in Seoul, Korea. The protocol was approved by the Institutional Review Board of Severance Hospital and the study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice standard (approval number: 4-2013-0311). The ClinicalTrial.gov registration number was NCT01921647. Written informed consent was obtained from each subject before their enrollment into the study.

**Table 1.** Study design

Sequence	No. of subjects	Period 1	Period 2	Period 3	Period 4
1	8	YH + A + C	YH	A	C
2	8	A	YH + A + C	C	YH
3	8	C	A	YH	YH + A + C
4	8	YH	C	YH + A + C	A

YH, YH4808 200 mg tablet, single administration of 1 tablet; A, amoxicillin 500 mg capsule, single administration of 2 capsules; C, clarithromycin 500 mg tablet, single administration of 1 tablet; YH + A + C, single co-administration of YH4808 200 mg 1 tablet, amoxicillin 500 mg 2 capsules, clarithromycin 500 mg 1 tablet.

### Study participants

Healthy Korean volunteers aged 20–55 years, with a body weight of at least 55 kg and a body mass index (BMI) of 18.5–25.0 kg/m<sup>2</sup> were eligible in this study. The screening included documenting the medical history, physical examination, 12-lead electrocardiography (ECG), vital signs and clinical laboratory tests. Persons with a history of GI disease or major surgery that could affect the absorption of investigational products (IPs) or those who were hypersensitive to the IP component were excluded from the study. Heavy smokers (more than 10 cigarettes a day), habitual drinkers, and those who consumed excessive caffeine were ineligible. Consumption of grapefruits juice, as well as prescription drugs or herbal medicines that could potentially interact with YH4808 was prohibited.

### Study design

This study had a randomized, open-label, single-dose, 4-treatment, 4-period, Latin-square (4 × 4) crossover design with a 21-day washout interval between each treatment period. A total of 32 subjects were randomly divided into 4 treatment sequence groups. The study regimens are presented in **Table 1**.

On day 1, 22, 43 and 64, a single dose of a tablet of 200 mg YH4808 or 2 capsules of 500 mg amoxicillin (Pamoxin<sup>®</sup>; Dong Wha Pharm. Co., Ltd., Seoul, Korea) or a tablet of 500 mg clarithromycin (Klaricid<sup>®</sup>; Abbott Korea, Seoul, Korea) was orally administered either as monotherapy or in combination as triple therapy after a standard meal with 240 mL of water. Water intake was restricted for 1 h after IP administration. Subjects were not allowed to consume anything except water for 4 h after IP administration and maintained an upright or 45° reclining sitting posture.

### PK sampling and analytical methods

Peripheral venous blood samples were collected at 0 (pre-dose) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 h after IP administration on day 1, 22, 43, and 64. The samples were centrifuged for 10 min at 4°C at 1,910 g, and the supernatants were separated for storage at -70°C or below.

Plasma concentrations of YH4808, the YH4808 metabolites M3 and M8, amoxicillin, clarithromycin were determined by high-performance liquid chromatography (LC-20AD, Shimadzu, Kyoto, Japan) coupled with mass spectrometry (API 4000 Triple Quad; AB Sciex, Washington, D.C., USA) based on validated analytical procedures adopted by the Korean Ministry of Food and Drug Safety. The plasma concentration of 14-hydroxyclearithromycin was detected by liquid chromatography (UPLC; Waters, Milford, MA, USA) coupled with mass spectrometry (TQ-S; Waters). The calibration curves were linear in the range of 0.2–1,000 ng/mL for YH4808 and M3 and 5–4,000 ng/mL for M8 (correlation coefficient,  $r > 0.9959$ ) with the lower limit of quantification (LLOQ) values of 0.2 ng/mL and 5 ng/mL, respectively.

The assay ranges were 50–40,000 ng/mL for amoxicillin 10–5,000 ng/mL for clarithromycin and its metabolite ( $r > 0.9989$ ) with the LLOQ values of 50 ng/mL and 10 ng/mL, respectively. The assay accuracy was within 92.2–106.9% for YH4808 and its metabolite, 98.3–102.9% for amoxicillin, and 97.5–101.6% for clarithromycin and its metabolite; the precision coefficients of variation were all within the acceptance criteria of  $< 15\%$  ( $< 20\%$  at the LLOQ level).

### PK analysis

A non-compartmental analysis using WinNonlin® Version 6.3 (Pharsight, Mountain View, CA, USA) was performed to calculate the following PK parameters: the maximum plasma concentration ( $C_{\max}$ ), time to reach  $C_{\max}$  ( $T_{\max}$ ), area under the time-concentration curve from time zero to time of the last quantifiable concentration, ( $AUC_{\text{last}}$ ), AUC from time zero extrapolated to the infinite time ( $AUC_{\text{inf}}$ ), terminal elimination half-life ( $t_{1/2}$ ).  $C_{\max}$  and  $T_{\max}$  were directly derived from actual measurements;  $t_{1/2}$  was calculated from the ratio of the natural logarithm of 2 and the terminal elimination rate constant, and AUC was calculated using the linear trapezoidal rule.

### Safety assessment

Safety monitoring was performed throughout the study for all subjects who had received at least one IP dose. Safety was evaluated by monitoring adverse events (AEs), vital signs, physical examination, clinical laboratory tests (hematology, blood chemistry, and urinalysis), and 12-lead ECG. Characteristics of AEs including severity and causality were determined according to the treatment group in relation to the last IP administration by investigators.

### Statistical analysis

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). Baseline demographics, such as age, weight, height, and BMI along with PK parameters, were summarized using descriptive statistics. The log-transformed primary PK parameters ( $C_{\max}$  and  $AUC_{\text{last}}$ ) between single and triple administration of each IP were compared by developing a mixed-effects model, using the period, sequence, and treatment as fixed effects and the subjects nested within the sequence as a random effect. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) of the primary PK parameters between 2 treatment groups (single vs. triple therapy) were estimated to evaluate PK drug interactions. A P-value  $< 0.05$  was considered statistically significant. The number of subjects with AEs was compared among the 4 treatment sequences using Cochran's Q test.

## RESULTS

### Study subjects

A total of 33 healthy male subjects enrolled, and 32 subjects received an IP treatment at least once during the study. Four subjects withdrew from the study, and 28 subjects completed all study procedures. The demographics summary of each treatment sequence is presented in **Table 2**.

### PK analysis

The calculated PK parameters of YH4808 and its metabolites for the monotherapy or the triple therapy with amoxicillin and clarithromycin are summarized in **Table 3**, and the mean plasma concentration-time profiles are shown in **Figure 1**. During the triple therapy, the YH4808 and M3 exposures were higher, whereas the M8 exposure was lower compared

**Table 2.** Demographic characteristics of subjects

Demographic variable	Treatment sequence (mean ± standard deviation)				Total (n = 32)
	Sequence 1 (n = 8)	Sequence 2 (n = 8)	Sequence 3 (n = 8)	Sequence 4 (n = 8)	
Age (yr)	29.5 ± 4.3	28.1 ± 4.9	26.9 ± 4.1	28.1 ± 4.3	28.2 ± 4.3
Weight (kg)	66.8 ± 6.9	67.0 ± 9.6	68.3 ± 4.8	68.1 ± 8.7	67.5 ± 7.4
Height (cm)	172.6 ± 4.9	172.4 ± 7.4	175.2 ± 6.7	174.6 ± 8.1	173.7 ± 6.7
BMI (kg/m <sup>2</sup> )	22.3 ± 1.4	22.4 ± 1.8	22.3 ± 1.9	22.2 ± 1.8	22.3 ± 1.6
Sex, No. (%)					
Male	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

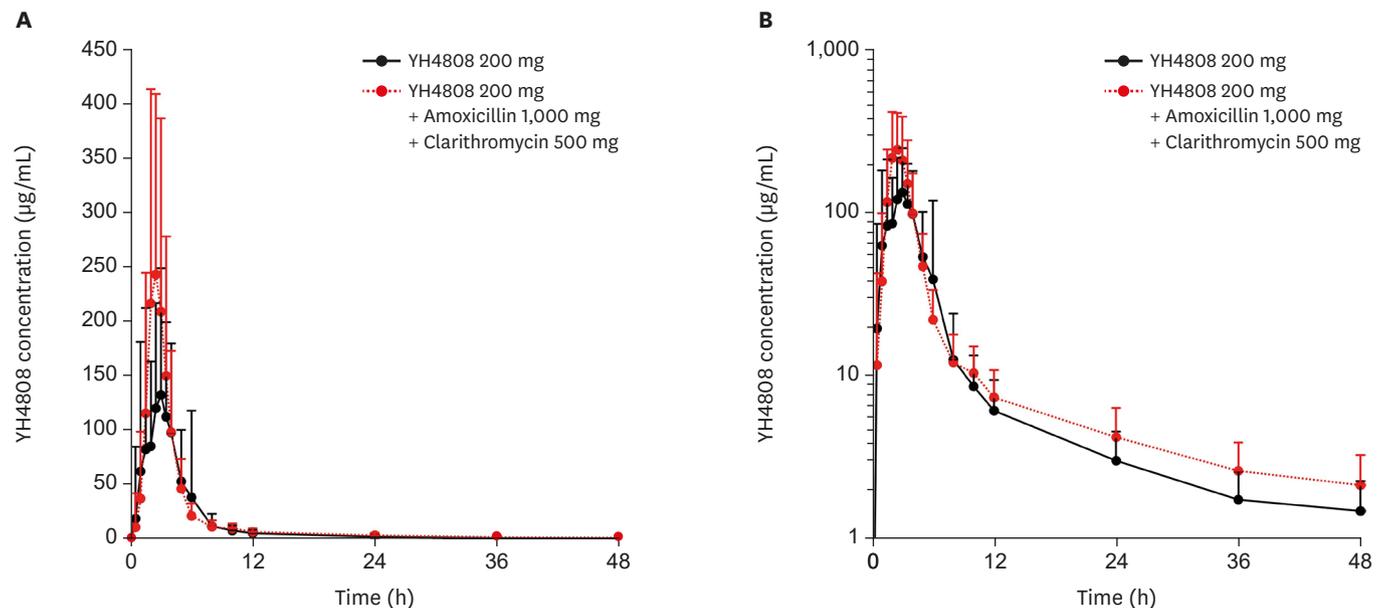
Order of treatment periods: Sequence 1, YH + A + C, YH, A, C; Sequence 2, A, YH + A + C, C, YH; Sequence 3, C, A, YH, YH + A + C; Sequence 4, YH, C, YH + A + C, A. BMI, body mass index; YH, YH4808; A, amoxicillin; C, clarithromycin.

**Table 3.** Comparison of pharmacokinetic parameters of YH4808 and its metabolites

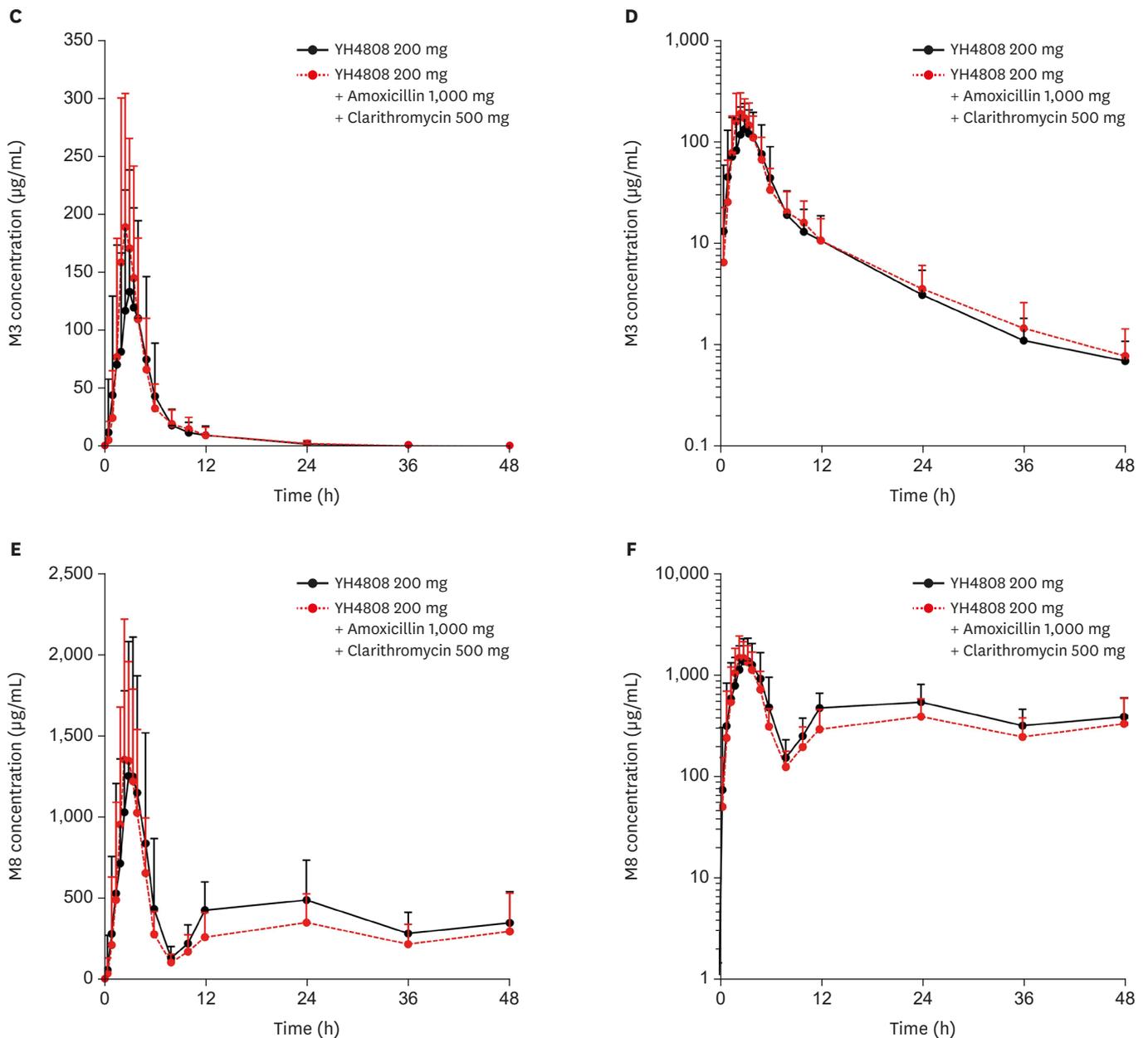
Substance	PK parameter	Mean ± standard deviation		GMR% (90% CI)
		YH momotherapy (n = 28)	YH + A + C (n = 28)	
YH4808	T <sub>max</sub> (h)*	3.00 (1.00–6.00)	2.50 (1.00–4.00)	
	C <sub>max</sub> (µg/L)	239.00 ± 135.59	356.60 ± 202.39	1.4856 (1.3022–1.6948)
	AUC <sub>last</sub> (µg × h/L)	629.90 ± 289.35	823.77 ± 411.27	1.2908 (1.1822–1.4094)
	AUC <sub>inf</sub> (µg × h/L)	678.17 ± 310.47	897.30 ± 441.50	
	t <sub>1/2</sub> (h)	22.33 ± 3.68	23.18 ± 4.97	
M3	T <sub>max</sub> (h)*	3.00 (1.00–6.00)	2.50 (1.00–4.00)	
	C <sub>max</sub> (µg/L)	210.84 ± 105.55	257.95 ± 127.03	1.2334 (1.0966–1.3872)
	AUC <sub>last</sub> (µg × h/L)	689.58 ± 381.58	782.89 ± 395.16	1.1602 (1.0751–1.2520)
	AUC <sub>inf</sub> (µg × h/L)	700.36 ± 388.96	797.49 ± 404.66	
	t <sub>1/2</sub> (h)	11.19 ± 2.87	12.33 ± 3.52	
M8	T <sub>max</sub> (h)*	3.00 (1.00–6.00)	2.75 (1.50–4.00)	
	C <sub>max</sub> (µg/L)	1,942.45 ± 700.43	1,812.82 ± 716.84	0.9366 (0.8376–1.0473)
	AUC <sub>last</sub> (µg × h/L)	20,025.15 ± 6,934.66	15,826.05 ± 6,623.11	0.7744 (0.7340–0.8171)

\*Values are presented as median (minimum–maximum).

YH, YH4808 200 mg tablet, single administration of 1 tablet; A, amoxicillin 500 mg capsule, single administration of 2 capsules; C, clarithromycin 500 mg tablet, single administration of 1 tablet; YH + A + C, single co-administration of YH4808 200 mg 1 tablet, amoxicillin 500 mg 2 capsules, clarithromycin 500 mg 1 tablet; PK, pharmacokinetic; GMR, geometric mean ratio; CI, confidence interval; T<sub>max</sub>, time to reach maximum plasma concentration; C<sub>max</sub>, maximum plasma concentration; AUC<sub>last</sub>, area under the time-concentration curve from time zero to time of the last quantifiable concentration; AUC<sub>inf</sub>, area under the time-concentration curve from time zero extrapolated to the infinite time; t<sub>1/2</sub>, terminal elimination half-life.



**Figure 1.** Plasma concentration-time profiles of YH4808 administered as single or triple therapy were plotted using (A) linear and (B) log-linear scales; M3, using (C) linear and (D) log-linear; M8 using (E) linear and (F) log-linear scales. (continued to the next page)



**Figure 1.** (Continued) Plasma concentration-time profiles of YH4808 administered as single or triple therapy were plotted using (A) linear and (B) log-linear scales; M3, using (C) linear and (D) log-linear; M8 using (E) linear and (F) log-linear scales.

with those during the YH4808 single therapy. The triple-to-single therapy GMRs (90% CIs) of YH4808  $C_{max}$  and  $AUC_{last}$  were 1.4856 (1.3022–1.6948) and 1.2908 (1.1822–1.4094), respectively; the corresponding M3  $C_{max}$  and  $AUC_{last}$  GMRs were 1.2334 (1.0966–1.3872) and 1.1602 (1.0751–1.2520), and those of M8 were 0.9366 (0.8376–1.0473) and 0.7744 (0.7304–0.8171), respectively.

The mean plasma concentration-time profiles of amoxicillin, clarithromycin and 14-hydroxyclearithromycin, given separately or as triple therapy, are shown in **Figures 2 and 3**. The PK parameters are summarized in **Table 4**. The triple-to-single therapy GMRs (90%

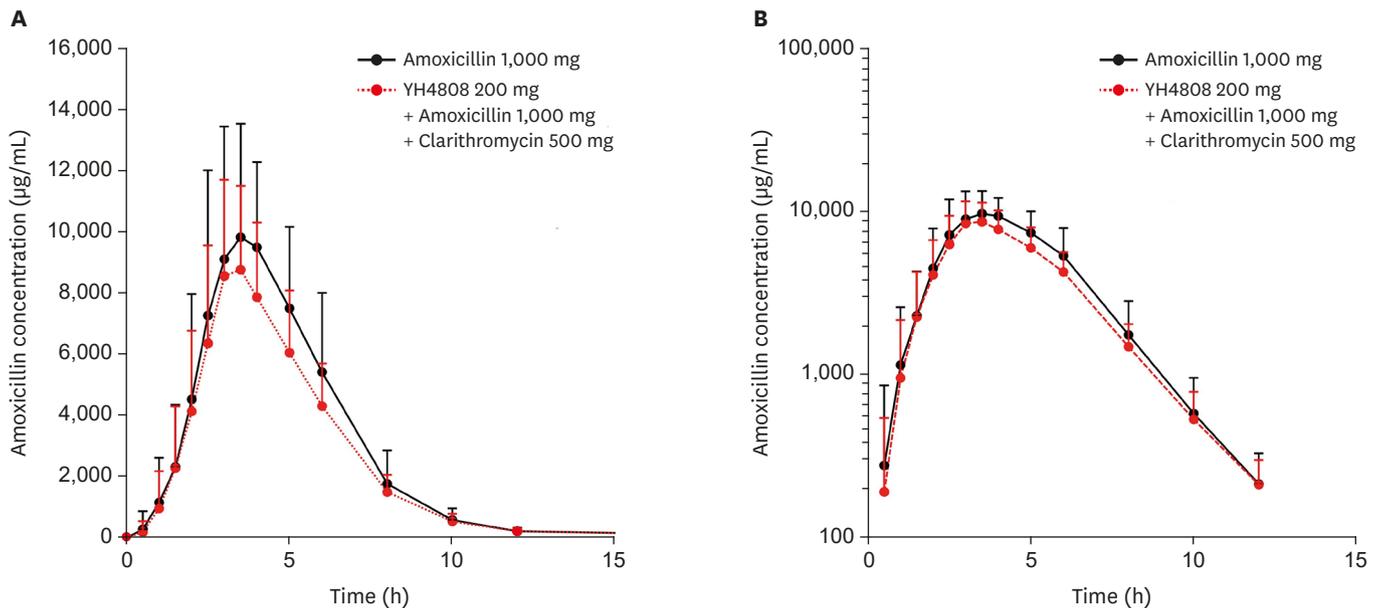


Figure 2. Plasma concentration-time profiles of amoxicillin administered as single or triple therapy were plotted using (A) linear and (B) log-linear scales.

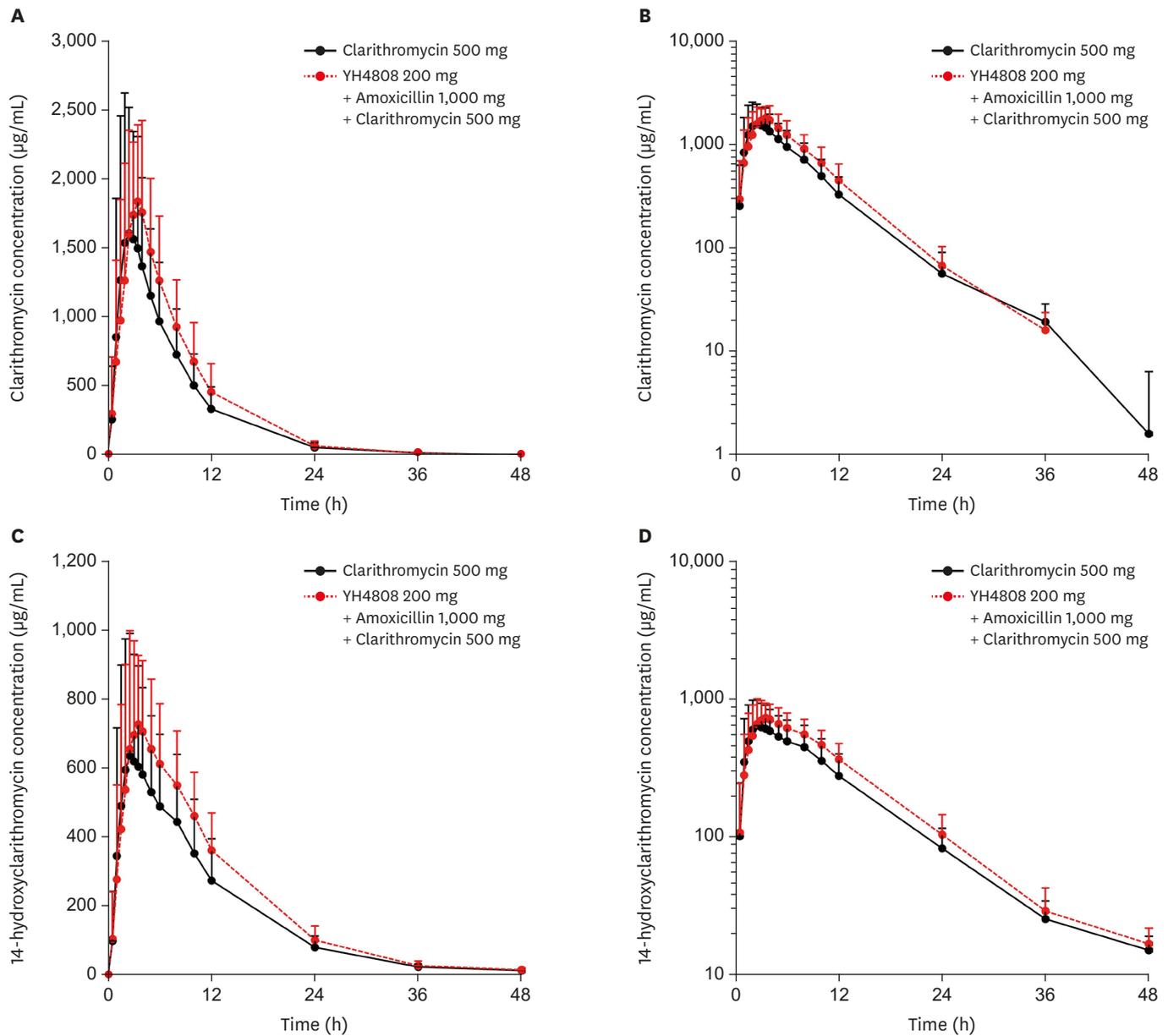
CI) of amoxicillin  $C_{max}$  and  $AUC_{last}$  were 0.7855 (0.7243–0.8518) and 0.8437 (0.7980–0.8919), respectively. The corresponding clarithromycin  $C_{max}$  and  $AUC_{last}$  GMRs were 1.2736 (1.0449–1.5224) and 1.3047 (1.1104–1.5330), and those of 14-hydroxyclearithromycin were 1.2310 (1.0556–1.4356) and 1.3237 (1.1428–1.5332), respectively. For the PK parameters of YH4808, amoxicillin, clarithromycin and its metabolites, there were no statistically significant period and sequence effects.

Table 4. Comparison of pharmacokinetic parameters of amoxicillin, clarithromycin and its metabolite 14-hydroxyclearithromycin

Substance	PK parameter	Mean ± standard deviation		GMR% (90% CI)
		A or C monotherapy (n = 28)	YH + A + C (n = 28)	
Amoxicillin	$T_{max}$ (h)*	3.50 (2.00–6.00)	3.02 (2.50–4.00)	
	$C_{max}$ (µg/L)	12,440.67 ± 3,437.17	9,854.51 ± 2,779.28	0.7855 (0.7243–0.8518)
	$AUC_{last}$ (µg × h/L)	43,758.42 ± 6,524.63	37,478.01 ± 8,792.35	0.8437 (0.7980–0.8919)
	$AUC_{inf}$ (µg × h/L)	44,199.16 ± 6,611.36	37,932.05 ± 8,888.48	
	$t_{1/2}$ (h)	1.44 ± 0.21	1.47 ± 0.23	
Clarithromycin	$T_{max}$ (h)*	2.50 (1.00–5.00)	3.00 (1.50–5.00)	
	$C_{max}$ (µg/L)	2,064.95 ± 1,029.66	2,317.80 ± 631.43	1.2736 (1.0449–1.5224)
	$AUC_{last}$ (µg × h/L)	12,807.19 ± 5,731.05	15,266.61 ± 4,304.77	1.3047 (1.1104–1.5330)
	$AUC_{inf}$ (µg × h/L)	13,021.58 ± 5,778.98	15,448.02 ± 4,299.87	
	$t_{1/2}$ (h)	4.84 ± 0.91	4.46 ± 0.63	
14-hydroxyclearithromycin	$T_{max}$ (h)*	2.50 (1.00–5.00)	3.00 (1.00–5.00)	
	$C_{max}$ (µg/L)	754.65 ± 361.84	857.83 ± 291.38	1.2310 (1.0556–1.4356)
	$AUC_{last}$ (µg × h/L)	7,878.64 ± 3,332.11	9,580.30 ± 2,539.61	1.3237 (1.1428–1.5332)
	$AUC_{inf}$ (µg × h/L)	8,088.49 ± 3,308.15	9,823.31 ± 2,532.30	
	$t_{1/2}$ (h)	8.81 ± 2.91	9.79 ± 3.69	

\*Values are presented as median (minimum–maximum).

YH, YH4808 200 mg tablet, single administration of 1 tablet; A, amoxicillin 500 mg capsule, single administration of 2 capsules; C, clarithromycin 500 mg tablet, single administration of 1 tablet; YH + A + C, single co-administration of YH4808 200 mg 1 tablet, amoxicillin 500 mg 2 capsules, clarithromycin 500 mg 1 tablet; PK, pharmacokinetic; GMR, geometric mean ratio; CI, confidence interval;  $T_{max}$ , time to reach maximum plasma concentration;  $C_{max}$ , maximum plasma concentration;  $AUC_{last}$ , area under the time-concentration curve from time zero to time of the last quantifiable concentration;  $AUC_{inf}$ , area under the time-concentration curve from time zero extrapolated to the infinite time;  $t_{1/2}$ , terminal elimination half-life.



**Figure 3.** Plasma concentration-time profiles of clarithromycin administered as single or triple therapy were plotted using (A) linear and (B) log-linear scales; 14-hydroxyclearithromycin using (C) linear and (D) log-linear scales.

### Safety

A total of 16 AEs occurred in 11 subjects who received an IP treatment at least once. Clinically significant changes in the vital signs, physical examination, 12-lead ECGs, or clinical laboratory test results were considered as AE. All observed AEs were mild, and subjects recovered without complications. There was no statistically significant difference in the number of subjects with AE among the treatment groups (Cochran's Q test:  $P = 0.392$ ). Four cases of AEs in 6 subjects were assessed to be associated with the IP treatment and considered as adverse drug reaction. The most commonly reported adverse drug reaction were headache (2 cases).

## DISCUSSION

*H. pylori* infection is one of the main causes of various GI diseases, including gastric cancer. In countries with a high prevalence of *H. pylori* infection, such as the Korea, China, and Japan, the recommended treatment option is a triple combination regimen of PPI, amoxicillin, and clarithromycin [13,14]. PPIs are administered as prodrugs in the form of chiral sulfoxide molecules that target the parietal cells. These enantiomers diffuse across the secretory membrane into canalicular lumen where the acidity, which is well below pH 2, chemically converts the prodrugs molecules into achiral sulfenamides that react with proton pumps [15]. Unlike PPIs, P-CAB agents do not undergo a chemical conversion. They directly inhibit H<sup>+</sup>/K<sup>+</sup>-ATPase by ionically binding at or near the potassium binding site in a competitive manner, which blocks gastric acid secretion by direct and reversible mechanism. P-CABs are lipophilic, weak bases with a high pKa that are stable at the low gastric pH, which facilitates their accumulation in the parietal cell space, resulting in a fast onset of action and an efficient dose-response relationship [12]. Thus, P-CABs represent an attractive alternative to PPIs for treating acid-related diseases due to their favorable mechanism and advantageous properties.

This study assessed a new triple therapy regimen for *H. pylori* eradication by examining the potential interactions between amoxicillin, clarithromycin, and YH4808, a new P-CAB used instead of a currently recommended PPI. Interestingly, simultaneous administration of YH4808 with amoxicillin and clarithromycin elevated its exposure. *In vitro* studies demonstrated that YH4808 is metabolized to its main active metabolite M3 by CYP2B6, CYP2C8, and CYP2D6 and to M8 by CYP1A2, 2C9, 2C19, 2D6, and 3A4 [11]. However, considering that in the triple therapy of this study, the AUC<sub>last</sub> of M8 decreased by 22.6%, whereas that of YH4808 and M3 increased by 29.1% and 16.0% respectively, the inhibition of CYP450 3A4 by clarithromycin might have potentially prevented a faster decomposition of the parent YH4808 and diverted it to other metabolic pathways, such as to the conversion to M3. Furthermore, amoxicillin might also have contributed to the stabilized exposure of YH4808, based on a report showing that amoxicillin inhibited CYP2C8-mediated aminopyrine N-demethylation [16]. Since CYP2C8 is at least partially involved in the metabolism of YH4808 to M3, it is possible that amoxicillin contributed to the increased exposure of YH4808 during the triple therapy.

In contrast, the amoxicillin exposures decreased by approximately 20% during the combination therapy, and YH4808 might have contributed to this effect for 2 reasons. First, the solubility of amoxicillin is lowest at pH 4–6 [17], which could have decreased the absorption of amoxicillin due to the rapid increase in gastric pH by simultaneous administration of YH4808. Secondly, YH4808 could have diminished the reabsorption of amoxicillin in the renal tubules through peptide transporter inhibition, thereby facilitate the excretion by kidneys [18]. A previous drug interaction study with another P-CAB, namely vonoprazan, in place of YH4808 showed increases in exposure of vonoprazan and clarithromycin, whereas amoxicillin exposure remained unchanged [19]. The vonoprazan used in that study doesn't seem to be involved in peptide transporters in kidneys.

Although clarithromycin is known to be rapidly and almost completely absorbed from the GI tract, extensive first-pass metabolism decreases its bioavailability to 50–55% [20]. During the triple therapy in our study, exposures of clarithromycin and its metabolite increased by approximately 20–30%. Since the pKa of clarithromycin is 8.99, the increase in gastric pH after the administration of YH4808 could have potentially increased its absorption because

more clarithromycin molecules might have remained unionized and in a chemically stable form at the higher pH. However, as indicated above, clarithromycin absorption typically proceeds to near completion and is probably not further increased by raising the pH. As a substrate of CYP3A4, clarithromycin is metabolized mainly by this enzyme. This could suggest that the metabolism of clarithromycin by CYP3A was diminished during triple therapy. The production of its 2 main metabolites, the active 14-hydroxyclearithromycin and the inactive N-desmethyl-clarithromycin, can be suppressed by CYP3A inhibition [21]. However, our results showed the exposures of both parent compound and major metabolite increased which cannot be explained by a simple inhibitory action on CYP3A by YH4808. A previous study in triple therapy with vonoprazan had the similar result but the underlying mechanisms were not clearly understood [19]. However, *in vitro* metabolic reaction phenotyping studies showed that YH4808 had a moderate inhibitory effect on the phase I and II hepatic enzymes including CYP3A [11]. Increased exposures of clarithromycin and its active metabolite, 14-hydroxyclearithromycin which has an additive effect on the parent compound, could potentiate the clinical outcome of *H. pylori* eradication [22].

We found that the drug interactions between the 3 components of the new combination therapy caused minor PK alterations. However, in most drug interaction studies, exposure increases of less than 2-fold are considered tolerable for combination regimens without dose modification. A previous study of YH4808 with a higher dose, 400 mg for multiple and 800 mg for single dosing, showed no safety and tolerability issue. Hence, the results of our study provide supportive evidence that combination regimens of YH4808, amoxicillin, and clarithromycin, can be used safely without dose modification [9].

In conclusion, there were no clinically significant alterations of the PK profiles when YH4808, used in place of a PPI, amoxicillin and clarithromycin were administered in combination, and no safety concerns were raised. Thus, YH4808 may serve as a safe substitute for a PPI in the currently recommended triple therapy regimens for *H. pylori* eradication.

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