Original Research

Pharmacokinetic Interactions between Tegoprazan and Metronidazole/Tetracycline/Bismuth and Safety Assessment in Healthy Korean Male Subjects

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ABSTRACT

Purpose: Tegoprazan is a potassium-competitive acid blocker used for gastric acid suppression, which may be used with *Helicobacter pylori* eradication therapies. The goal of this study was to evaluate the pharmacokinetic interaction between tegoprazan and triple-antibiotic therapy containing metronidazole, tetracycline, and bismuth.

Methods: : An open-label, 2-cohort, randomized, multiple-dose, crossover study was conducted in healthy subjects. In cohort 1, tegoprazan (100 mg/d) was administered orally with or without triple-antibiotic therapy (1500 mg/d metronidazole, 2000 mg/d tetracycline, and 1200 mg/d bismuth) for 7 days in each period. In cohort 2, triple-antibiotic therapy was administered orally with or without tegoprazan for 7 days in each period. Pharmacokinetic blood samples were collected within 24 h after the last dose. Safety assessments were performed.

Findings: : Eleven cohort 1 subjects and ten cohort 2 subjects were included in the pharmacokinetic analysis. The AUC_{τ} and C_{max} at steady state geometric mean ratios (90% CIs) were 0.78 (0.73−0.83) and 0.75 (0.68−0.82) for tegoprazan; 0.77 (0.68−0.88) and 0.84 (0.72−0.98) for tegoprazan metabolite M1; 1.03 (0.98−1.08) and 1.08 (0.99−1.18) for metronidazole; 0.63 (0.56−0.70) and 0.64 (0.56−0.74) for tetracycline; and 1.55 (0.99−2.44) and 1.38 (0.72−2.66) for bismuth, respectively. All reported adverse events were mild.

Implications: Changes in the tegoprazan, tetracycline, and bismuth pharmacokinetic parameters were detected after concurrent administration. These changes were considered mainly due to the pharmacodynamic effect of tegoprazan. The adverse events were predictable and reported as frequent adverse events during triple-antibiotic therapy. There were no significant differences in safety or tolerability between quadruple therapy, including tegoprazan and triple-antibiotic therapy. ClinicalTrials.gov identifier: NCT04066257. (*Clin Ther*. 2021;43:722−734) © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: bismuth, *Helicobacter pylori*, metronidazole, pharmacokinetic drug interaction, tegoprazan, tetracycline.

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INTRODUCTION

Gastric H^+,K^+-adenosine triphosphatase (ATPase) is the primary target for the treatment of acid-related disorders. Proton-pump inhibitors (PPIs) have been used for the treatment of a wide range of acid-related diseases, including gastroesophageal reflux disease, gastric ulcers, and *Helicobacter pylori* eradication therapy.[1] However, conventional PPIs require several days to show maximal effects and have a slow onset of pharmacologic action.[1–4] To overcome the limitations of conventional PPIs, new H+,K+-ATPase inhibitors with fast onset of pharmacologic action have been developed. One of these new H+,K+-ATPase inhibitors is the potassium-competitive acid blocker (P-CAB).

P-CABs are a class of agents that inhibit gastric H^+,K^+-ATPase. Unlike conventional PPIs inhibiting H^+,K^+-ATPase by irreversible covalent bonds, P-CABs have a competitive and reversible manner by binding to the potassium-binding site of the enzyme and exhibit almost complete inhibition of gastric acid secretion.[5–7] P-CABs have a rapid onset of action, exhibit faster gastric pH inhibition than PPIs,[6] and are highly accumulated and slowly excreted. Because P-CABs have a potent and long-lasting effect, they are expected to replace some of the outdated therapies for acid-related diseases.[8]

Tegoprazan, a novel P-CAB, was developed by HK inno.N Corp. (Seoul, Republic of Korea). Tegoprazan is metabolized mainly by CYP3A4 to metabolite M1 (desmethyl tegoprazan) (Figure 1). The metabolic ratio of tegoprazan to metabolite M1 is approximately 1.44−1.52.[9] According to unpublished nonclinical data, the inhibitory activity (50% inhibition) of tegoprazan and metabolite M1 against porcine gastric H^+,K^+-ATPase was evaluated as 0.53 μM and 6.19 μM, respectively. In previous pharmacokinetic and pharmacodynamic clinical studies, tegoprazan showed rapid and potent gastric acid suppression.[10,11]

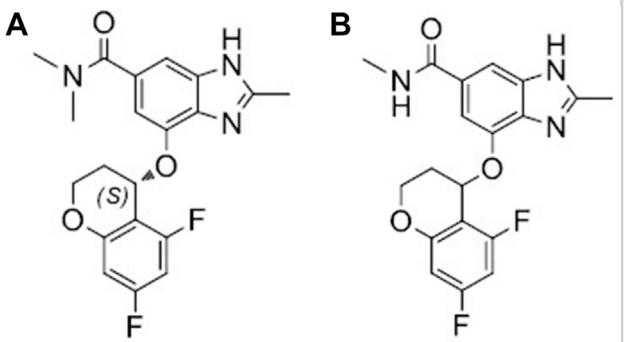

Figure 1. Structure of tegoprazan (A) and tegoprazan metabolite M1 (B).

Tegoprazan has been approved in the Republic of Korea for the treatment of gastroesophageal reflux disease and gastric ulcers. It is speculated that tegoprazan therapy could also be used to treat various diseases related to gastric acid, including *H pylori* eradication, and the eradication of *H pylori* is currently aimed at an additional indication of tegoprazan therapy. Especially in the Republic of Korea, where the *H pylori* infection rate in the general population is >40%, the importance of eradication therapy for this infection is gaining evidence.[12]

H pylori has been identified as a major factor in the pathogenesis of gastritis, peptic ulcers, and gastric cancer.[13] As a first-line treatment for *H pylori* infection, triple-antibiotic therapy with PPIs, amoxicillin, and clarithromycin has been recommended worldwide.[14] PPIs play major roles in eradication therapy by reducing gastric acid secretion and increasing the bioavailability and activities of antibiotics.[15] However, eradication via conventional triple-antibiotic therapy has decreased due to resistance against antibiotics[16]; this resistance was found in almost all antibiotics used in *H pylori* eradication, including clarithromycin and amoxicillin. Because of the increased antibiotic resistance, new regimens are recommended in some cases; for example, in regions suspected to have high clarithromycin resistance, quadruple therapy with bismuth, metronidazole, and tetracycline given together with a PPI is currently recommended as an alternative regimen.[17] Bismuth-based quadruple therapies, including the PPI regimen, were highly effective for treatments of *H pylori* infection.[18]

Due to several advantages of using P-CABs over conventional PPIs, bismuth quadruple therapy with P-CABs instead of PPIs may be useful in *H pylori* eradication. The present study evaluated the pharmacokinetic drug interaction between tegoprazan and metronidazole, tetracycline, and bismuth, as well as safety.

SUBJECTS AND METHODS

This study was approved by the Ministry of Food and Drug Safety of the Republic of Korea and the Institutional Review Board of Jeonbuk National University Hospital (Jeonju, Republic of Korea). It was conducted according to the Declaration of Helsinki for biomedical research involving human subjects and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all participants before screening.

Subjects

The study enrolled 32 healthy Korean male volunteers aged 19–55 years. The subjects were screened to confirm their health status by physical examination, vital sign measurement, 12-lead ECG, routine laboratory assessments (ie, hematology, chemistry, urinalysis, serology), and urea breath test performed within the 4 weeks before the first administration of the study drug. The following exclusion criteria were applied: evidence or history of clinically significant hematologic, renal, endocrine, respiratory, gastrointestinal track, urinary system, cardiovascular, liver, psychiatric, or neurologic disease; any surgical or medical condition that could affect drug absorption; hypersensitivity or history of sensitivity to the investigational product; and use of any prescription or over-the-counter medication within 10 days before the study.

The enrolled subjects were healthy and negative for *H pylori* infection. The subjects were asked to abstain from alcoholic beverages starting 24 h before hospitalization until the end of the last study period and to avoid smoking and the consumption of caffeine-containing foods during the hospitalization period.

Study Design

A 2-cohort, open-label, randomized, multiple-dose, crossover study was conducted in healthy subjects. Sixteen subjects were randomly assigned to 1 of the 2 sequences in each cohort. The subjects were hospitalized at the study site a day before drug administration. On day 1 to day 7, subjects received the investigational product assigned to the sequence group. In cohort 1, tegoprazan (50 mg) was administered orally BID (7 AM and 7 PM) with or without triple-antibiotic therapy for 7 days. The triple-antibiotic therapy consisted of metronidazole (500 mg) 3 times per day (7 AM, 1 PM, and 7 PM), tetracycline (500 mg) 4 times per day (7 AM, 1 PM, 7 PM, and 1 AM), and bismuth subcitrate potassium (300 mg, equivalent to 120 mg of bismuth oxide) 4 times per day (7 AM, 1 PM, 7 PM, and 1 AM) for 7 days. In cohort 2, triple-antibiotic therapy was administered orally with or without tegoprazan for 7 days in each period. Subjects received the investigational product assigned to the sequence group with 150 mL of water on day 1 to day 7. Standard meals were given 1 h after drug administration.

A heparin-locked catheter was inserted into a vein of the forearm of each subject for collection of blood samples. Blood samples were taken into EDTA tubes at the following scheduled times: before drug administration on day 1, day 5, day 6, and day 7 and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after drug administration on day 7 in each period. The subjects were discharged on the morning of day 8. A 14-day washout interval separated each of the treatment periods. The second study period was conducted on the same schedule as the first study period, with the exception of the assignment of the investigational product administered.

Safety and Tolerability Assessments

Subjects were continuously monitored by investigators throughout the study period. Adverse event (AE) monitoring, laboratory assessments (hematology, chemistry, and urinalysis), vital sign measurements, and physical examinations were performed at predefined regular intervals throughout the study.

Analytical Procedures

Blood samples were centrifuged (1800 *g* at 4 °C) for 10 min, and the plasma was immediately stored in polypropylene tubes at −70 °C until further analysis. The plasma concentrations of tegoprazan and tegoprazan metabolite M1 (the major metabolite of tegoprazan) in cohort 1 and concentrations of metronidazole, tetracycline, and bismuth in cohort 2 were analyzed. The quantification of tegoprazan, tegoprazan metabolite M1, metronidazole, and tetracycline was conducted by LC-MS/MS. The quantification of bismuth was conducted by inductively coupled plasma mass spectrometry.

For tegoprazan and metabolite M1, tegoprazan-d_6 was used as the internal standard. Chromatographic separation was performed by using a Poroshell 120 EC-C_{18} column (30 × 50 mm, 2.7 μm) at a flow rate of 0.3 mL/min. The mobile phases were 5 mM ammonium formate in water and acetonitrile (55:45, v/v). The multiple reaction monitoring transitions were *m/z* 388.0→220.1 for tegoprazan, 374.2 →206.1 for the tegoprazan metabolite M1, and 394.1→226.1 for the internal standard. The calibration curves for tegoprazan were linear over the calibration concentration range from 0.02 to 10 μg/mL for tegoprazan (r = 0.99956). The within-run and between-run accuracies for tegoprazan were 101.98%−108.67% (with a precision of 4.21%−5.48%) and 100.61%−104.74% (with a precision of 1.47%−4.19%), respectively. The calibration curves for tegoprazan metabolite M1 were linear over the calibration concentration range from 0.01 to 5 μg/mL (r = 0.99958). The within-run and between-run accuracies for tegoprazan metabolite M1 were 100.47%−105.33% (with a precision of 3.61%−4.21%) and 100.14%−103.83% (with a precision of 0.87%−3.40%), respectively.

For metronidazole, metronidazole-d_3 was used as the internal standard. Chromatographic separation was performed by using a Cadenza CD-C_{18} column (3.0 × 100 mm, 3.0 μm) at a flow rate of 0.3 mL/min. The mobile phases were 0.1% formic acid in water and acetonitrile (20:80, v/v). The multiple reaction monitoring transitions were *m/z* 172.2→128.3 for metronidazole and 175.0→131.2 for the internal standard. The calibration curves for metronidazole were linear over the calibration concentration range from 0.2 to 100 μg/mL (r = 0.99869). The within-run and between-run accuracies for metronidazole were 93.85%−99.16% (with a precision of 1.61%−4.18%) and 94.09%−104.36% (with a precision of 1.77%−4.89%), respectively.

For tetracycline, demeclocycline was used as the internal standard. Chromatographic separation was performed by using a Gemini 3 μm NX-C_{18} 110 Å column (100 × 2 mm, 3 μm) at a flow rate of 0.3 mL/min. The mobile phases were 0.1% formic acid in water and acetonitrile (85:15, v/v). The multiple reaction monitoring transitions were *m/z* 445.10→410.10 for tetracycline and 465.00→448.10 for the internal standard. The calibration curves for tetracycline were linear over the calibration concentration range from 0.02 to 10 μg/mL (r = 0.99924). The within-run and between-run accuracies for tetracycline were 99.67%−101.47% (with a precision of 2.08%−3.81%) and 98.15%−100.46% (with a precision of 1.58%−5.57%), respectively.

The quantification of bismuth was conducted by inductively coupled plasma mass spectrometry. For bismuth, thallium was used as the internal standard. Then, 4800 μL of 0.1% Triton X-100 in 0.5% nitric acid was added and filtered through a 0.22 μm nylon membrane. The calibration curves for bismuth were linear over the calibration concentration range from 0.5 to 100 ng/mL (r = 0.99979). The within-run and between-run accuracies for bismuth were 99.60%−102.88% (with a precision of 0.42%−0.60%) and 99.34%−100.62% (with a precision of 0.29%−2.45%), respectively.

Pharmacokinetic Assessments

The individual pharmacokinetic parameters were obtained with noncompartmental methods by using Phoenix WinNonlin 8.1 (Certara USA Inc, Princeton, New Jersey). The actual blood collection times were used in the pharmacokinetic analysis. C_{max} at steady state ($C_{ss,max}$), maximum concentration at steady state ($C_{ss,min}$), and time to reach $C_{ss,max}$ ($T_{ss,max}$) were obtained directly from the observed values. $C_{ss,av}$ is the average plasma concentration at steady state. AUC_τ was calculated by using the linear trapezoidal rule. According to the dosage interval, the AUC_{0-12} for tegoprazan and tegoprazan metabolite M1 and AUC_{0-6} for metronidazole, tetracycline, and bismuth were calculated. The $t_{1/2}$ of a substance is the amount of time required for the blood plasma concentration to decrease by 50% and is calculated as $\ln(2)/k_e$. The elimination rate constant (k_e) describes the rate of decrease in concentration per unit of time, which is estimated from the log-linear terminal part of the concentration−time curve as the slope of the natural logarithm of the concentration against time.

Statistical Analysis

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina). The pharmacokinetic parameters were summarized as the mean (SD), with the exception of T_{max}, for which median (minimum−maximum) values are given. The point estimate and 90% CIs for

Table I. Demographic characteristics of the study subjects. Values are given as mean (SD) unless otherwise indicated.

Parameter	Cohort 1 (n = 16)	Cohort 2 (n = 16)
Sex (male/female)	16/0	16/0
Age, y	24.19 (5.39)	23.69 (3.65)
Height, cm	172.07 (5.76)	174.99 (7.77)
Weight, kg	67.97 (8.94)	71.31 (7.80)
BMI, kg/m^2	22.89 (2.68)	23.23 (1.81)

the geometric mean ratios of $C_{ss,max}$ and AUC_τ values were assessed with an ANOVA by using a mixed effect model at a 5% significance level. The treatment, sequence, and period were used as fixed effects, and subjects nested within the treatment sequence were used as a random effect. To assess the steady-state concentration, the trough values were regressed over time, and the resultant slope was tested against the null hypothesis of zero slope. The logarithm of the 3 trough values (–48, –24, and 0 h) was used to regress over time.

RESULTS

Subject Population

In cohort 1, a total of 16 healthy male subjects were enrolled, among which 5 subjects were withdrawn

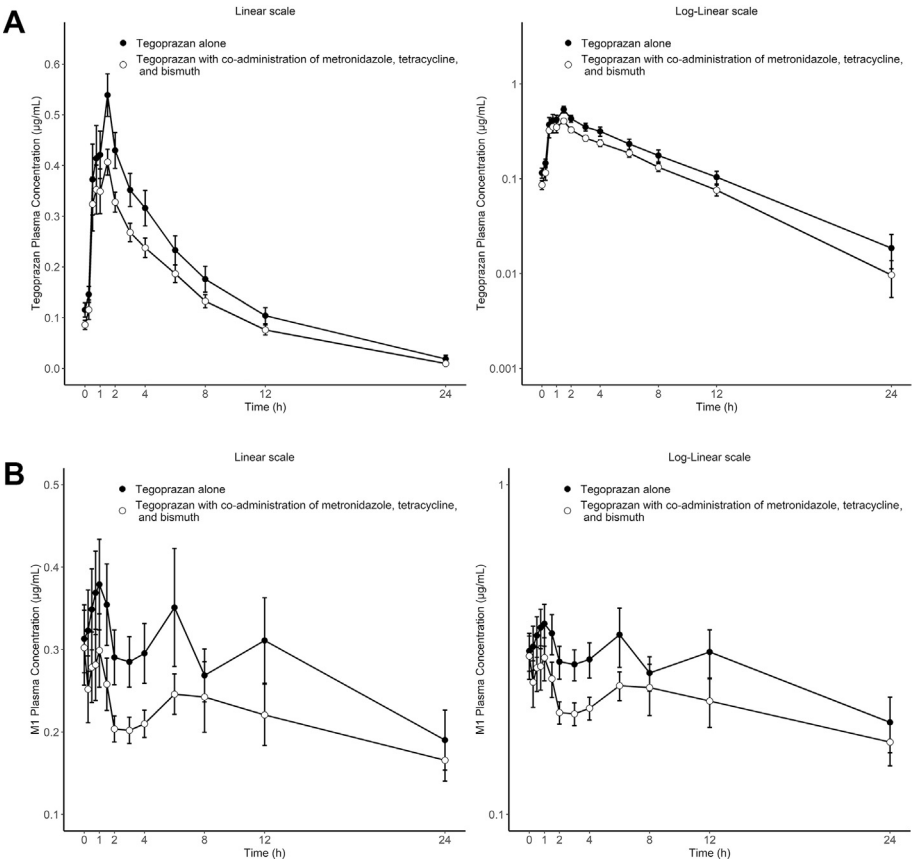

Figure 2. Plasma concentration profiles of tegoprazan (A) and tegoprazan metabolite M1 (B) after multiple oral administrations of tegoprazan with or without metronidazole, tetracycline, and bismuth (N = 11). Each point represents the arithmetic mean. Error bars represent the SEs.

Table II. Pharmacokinetic parameters of tegoprazan and tegoprazan metabolite M1 after multiple oral administrations with or without coadministration of metronidazole, tetracycline, and bismuth (N = 11). Values are presented as the mean (SD), except for T_{max} values, which are given as median [minimum−maximum].

Parameter	Tegoprazan Alone	Tegoprazan With Coadministration of Metronidazole, Tetracycline, and Bismuth
Tegoprazan		
AUC_{0-12}, h • μg/mL	3.02 (0.97)	2.34 (0.55)
$C_{ss,max}$, μg/mL	0.60 (0.12)	0.46 (0.10)
$C_{ss,min}$, μg/mL	0.10 (0.05)	0.08 (0.03)
$C_{ss,av}$, μg/mL	0.25 (0.08)	0.19 (0.05)
$T_{ss,max}$, h*	1.5 [0.5−1.5]	1.0 [0.5−2.0]
$t_{1/2}$, h	5.22 (1.35)	4.89 (0.95)
CL_{ss}/F, L/h	18.37 (6.56)	22.67 (6.02)
Tegoprazan metabolite M1		
AUC_{0-12}, h • μg/mL	3.70 (1.75)	2.81 (1.13)
$C_{ss,max}$, μg/mL	0.41 (0.22)	0.33 (0.15)
$C_{ss,min}$, μg/mL	0.31 (0.17)	0.22 (0.12)
$C_{ss,av}$, μg/mL	0.31 (0.15)	0.23 (0.09)

AUC_{0-12} = Area under the plasma concentration-time curve from time zero to 12 h at steady state; CL_{ss}/F = apparent clearance at steady state; $C_{ss,av}$ = average plasma concentration at steady state; $C_{ss,max}$ = maximum plasma concentration at steady state; $C_{ss,min}$ = minimum plasma concentration at steady state; $T_{ss,max}$ = time to $C_{ss,max}$; $t_{1/2}$ = Elimination half-life. *T_{max} values presented as median [min-max].

from the study due to withdrawal of consent, and 11 subjects were included in the pharmacokinetic set. In cohort 2, a total of 16 healthy male subjects were enrolled, among which 5 subjects were withdrawn during the treatment period due to withdrawal of consent and 1 subject was withdrawn due to AEs, and 10 subjects were included in the pharmacokinetic set. The characteristics of these subjects are summarized in Table I.

Pharmacokinetic Assessments

To determine the steady-state concentration, the logarithm of the 3 trough measurements was regressed over time. The 90% CIs for the exponential

Table III. The ratios and the 90% CIs of the geometric means for tegoprazan and tegoprazan metabolite M1 to tegoprazan with coadministration of metronidazole, tetracycline, and bismuth.

Parameter	N	Ratios	90% CIs
Tegoprazan			
AUC_{0-12}, h • μg/mL	11	0.7821	0.7333−0.8342
$C_{ss,max}$, μg/mL	11	0.7485	0.6847−0.8182
Tegoprazan metabolite M1			
AUC_{0-12}, h • μg/mL	11	0.7739	0.6779−0.8835
$C_{ss,max}$, μg/mL	11	0.8391	0.7165−0.9825

AUC_{0-12} = Area under the plasma concentration-time curve from time zero to 12 h at steady state; $C_{ss,max}$ = maximum plasma concentration at steady state.

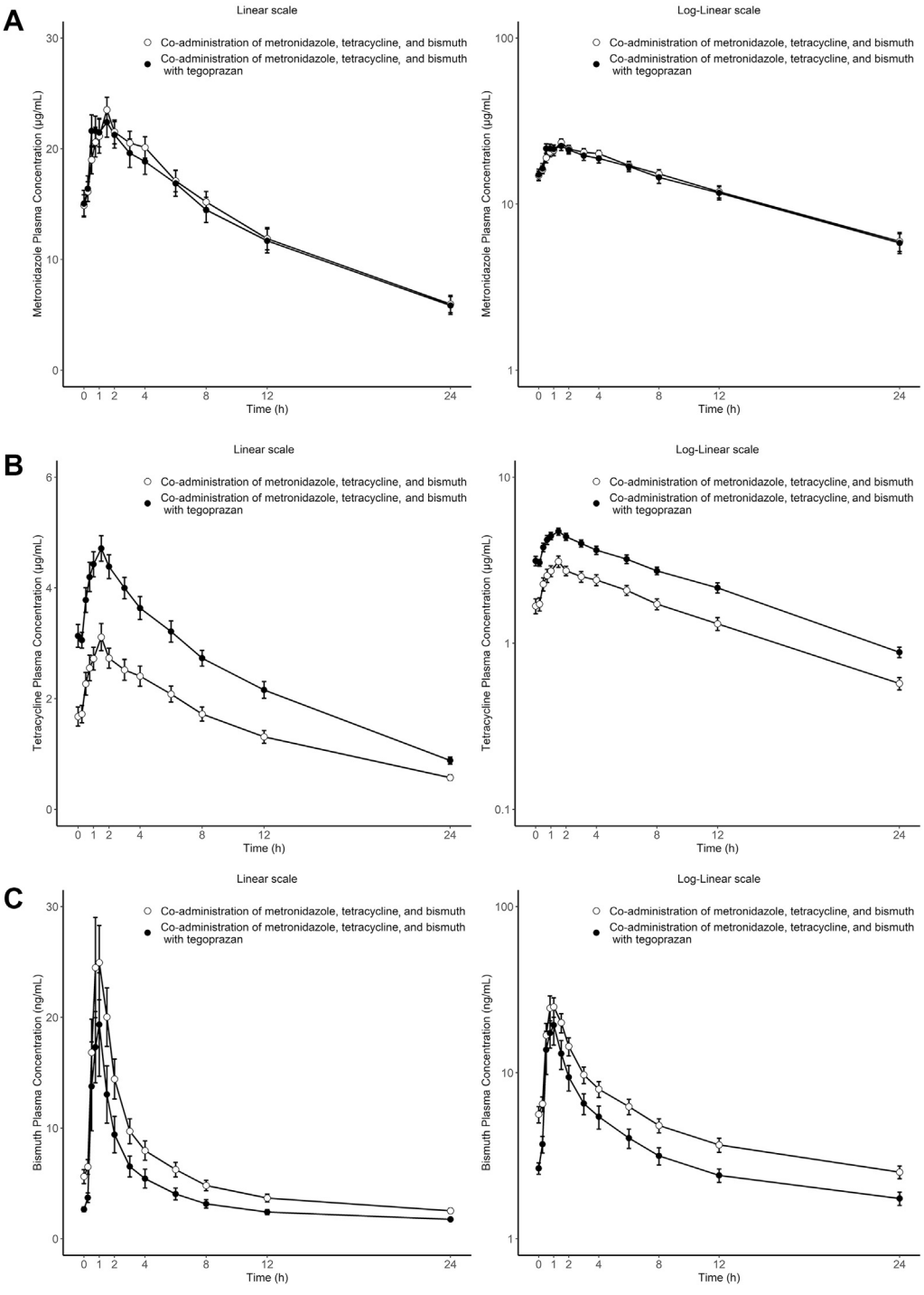

Figure 3. Plasma concentration profiles of metronidazole (A), tetracycline (B), and bismuth (C) after multiple oral administrations of metronidazole, tetracycline, and bismuth with or without tegoprazan (N = 10). Each point represents the arithmetic mean. Error bars represent the SEs.

of the slope over time included 1, indicating that a steady state was reached at day 7.

Figure 2 illustrates the plasma concentration−time curve of tegoprazan and tegoprazan metabolite M1 after multiple doses of tegoprazan with or without coadministration of metronidazole, tetracycline, and bismuth. The pharmacokinetic parameters of tegoprazan and tegoprazan metabolite M1 are summarized in Table II. The point estimates and the 90% CIs of the ratio of geometric means for tegoprazan alone to tegoprazan with coadministration of metronidazole, tetracycline, and bismuth for tegoprazan and M1 are summarized in Table III. The ratio of tegoprazan AUC_{0-12} and $C_{ss,max}$ decreased to 0.78 and 0.75, respectively, in the presence of metronidazole, tetracycline, and bismuth coadministration. The ratio of M1 AUC_{0-12} and $C_{ss,max}$ decreased to 0.77 and 0.84, respectively, in the presence of metronidazole, tetracycline, and bismuth coadministration.

Figure 3 illustrates the plasma concentration−time curves of metronidazole, tetracycline, and bismuth after multiple doses of coadministration of metronidazole, tetracycline, and bismuth with or without tegoprazan. The pharmacokinetic parameters of metronidazole,

Table IV. Pharmacokinetic parameters of metronidazole, tetracycline, and bismuth after multiple oral administrations with or without tegoprazan (N = 10). Values are presented as the mean (SD), except for T_{max} values presented as median [minimum−maximum].

Parameter	Coadministration of Metronidazole, Tetracycline, and Bismuth	Coadministration of Metronidazole, Tetracycline, and Bismuth With Tegoprazan
Metronidazole		
AUC_{0-6}, h • μg/mL	116.71 (22.47)	119.50 (17.51)
$C_{ss,max}$, μg/mL	23.37 (4.51)	24.99 (3.24)
$C_{ss,min}$, μg/mL	16.87 (3.68)	17.09 (3.08)
$C_{ss,av}$, μg/mL	19.45 (3.75)	19.92 (2.92)
$T_{ss,max}$, h	1.5 [0.5−2.0]	1.5 [0.75−4.0]
$t_{1/2}$, h	11.86 (2.52)	11.71 (2.78)
CL_{ss}/F, L/h	4.42 (0.80)	4.26 (0.58)
Tetracycline		
AUC_{0-6}, h • μg/mL	23.12 (3.70)	14.69 (3.33)
$C_{ss,max}$, μg/mL	4.78 (0.73)	3.13 (0.78)
$C_{ss,min}$, μg/mL	3.21 (0.61)	2.08 (0.46)
$C_{ss,av}$, μg/mL	3.85 (0.62)	2.45 (0.56)
$T_{ss,max}$, h	1.5 [1.0−1.5]	1.5 [1.0−2.0]
$t_{1/2}$, h	9.73 (1.25)	10.13 (1.87)
CL_{ss}/F, L/h	22.18 (3.86)	36.33 (11.65)
Bismuth		
AUC_{0-6}, h • ng/mL	48.57 (25.17)	70.77 (26.04)
$C_{ss,max}$, ng/mL	23.02 (15.84)	27.86 (13.72)
$C_{ss,min}$, ng/mL	4.04 (1.70)	6.25 (2.10)
$C_{ss,av}$, ng/mL	8.09 (4.20)	11.79 (4.34)
$T_{ss,max}$, h	0.75 [0.5−1.0]	0.88 [0.5−1.5]
$t_{1/2}$, h	24.27 (16.40)	17.71 (5.26)
CL_{ss}/F, L/h	6422.94 (3444.95)	3905.32 (1618.09)

AUC_{0-6} = Area under the plasma concentration-time curve from time zero to 6 h at steady state; CL_{ss}/F = apparent clearance at steady state; $C_{ss,av}$ = average plasma concentration at steady state; $C_{ss,max}$ = maximum plasma concentration at steady state; $C_{ss,min}$ = minimum plasma concentration at steady state; $T_{ss,max}$ = time to $C_{ss,max}$; $t_{1/2}$ = Elimination half-life.

tetracycline, and bismuth are summarized in Table IV. The point estimates and the 90% CIs of the ratio of geometric means of coadministration of metronidazole, tetracycline, and bismuth to coadministration of metronidazole, tetracycline, and bismuth with tegoprazan for metronidazole, tetracycline, and bismuth are summarized in Table V. There was no statistically significant effect of coadministration with tegoprazan on the metronidazole pharmacokinetic variables. The ratio of tetracycline AUC_{0-6} and $C_{ss,max}$ decreased to 0.63 and 0.64, respectively, in the presence of coadministration with tegoprazan. The bismuth AUC_{0-6} and $C_{ss,max}$ increased to 1.55 and 1.38 in the presence of coadministration with tegoprazan.

Safety and Tolerability

There were no serious AEs reported (Table VI). In cohort 1, a total of 48 cases of AEs in 12 subjects were reported during the study. AEs were reported for 12 cases in 4 subjects after administering tegoprazan alone treatment and 36 cases in 11 subjects after administering tegoprazan with metronidazole, tetracycline, and bismuth. In cohort 2, a total of 35 cases of AEs in 13 subjects were reported during the study. AEs were reported for 16 cases in 8 subjects after the coadministration of metronidazole, tetracycline, and bismuth and 19 cases in 9 subjects after administering tegoprazan with metronidazole, tetracycline, and bismuth. All AEs reported were considered mild. There were no clinically significant findings in the physical examinations, including changes in vital signs, ECG findings, or clinical laboratory evaluations.

DISCUSSION

We studied the pharmacokinetic interaction between tegoprazan and triple-antibiotic therapy after multiple administrations and safety in healthy Korean male subjects. In cohort 1, we studied the effect of triple-antibiotic therapy on the pharmacokinetics of tegoprazan. Tegoprazan is expected to be metabolized by cytochrome P450 3A4 in humans. The metabolite M1 is the major metabolite and was analyzed in this study. The AUC_{0-12} and $C_{ss,max}$ of tegoprazan and tegoprazan metabolite M1 decreased by 16%−25% when metronidazole, tetracycline, and bismuth were coadministered. The disposition patterns of tegoprazan and tegoprazan metabolite M1 were similar when tegoprazan was administered alone or when it was coadministered with triple-antibiotic therapy, and it is assumed that absorption of tegoprazan may be inhibited by coadministration with triple-antibiotic therapy. The mechanism of action for the decreased absorption of tegoprazan and metabolite M1 is not clear. To date, since the results of pharmacokinetic/pharmacodynamic clinical trials of tegoprazan have been only available for doses ≥50 mg, it is difficult to establish no-effect boundaries related to the exposure reduction of tegoprazan by triple-antibiotic therapy identified in this study.[19,20] The effect of decreased absorption on clinical response requires clinical studies in patients.

Table V. The ratios and the 90% CIs of the geometric means for metronidazole, tetracycline, and bismuth to coadministration of metronidazole, tetracycline, and bismuth with tegoprazan.

Parameter	N	Ratios	90% CIs
Metronidazole			
AUC_{0-6}, h • μg/mL	10	1.0310	0.9808−1.0839
$C_{ss,max}$, μg/mL	10	1.0805	0.9867−1.1831
Tetracycline			
AUC_{0-6}, h • μg/mL	10	0.6250	0.5614−0.6958
$C_{ss,max}$, μg/mL	10	0.6420	0.5598−0.7362
Bismuth			
AUC_{0-6}, h • ng/mL	10	1.5497	0.9854−2.4371
$C_{ss,max}$, ng/mL	10	1.3848	0.7210−2.6595

AUC_{0-6} = Area under the plasma concentration-time curve from time zero to 6 h at steady state; $C_{ss,max}$ = maximum plasma concentration at steady state.

Table VI. Adverse events per treatment.

Adverse Event	Cohort 1 (n = 16)				Cohort 2 (N = 16)			
	Tegoprazan Alone (n = 16)		Tegoprazan With Coadministration Of Metronidazole, Tetracycline, and Bismuth (n = 15)		Coadministration of Metronidazole, Tetracycline, and Bismuth (n = 14)		Coadministration of Metronidazole, Tetracycline, and Bismuth With Tegoprazan (n = 13)	
	Related	Not Related	Related	Not Related	Related	Not Related	Related	Not Related
Gastrointestinal disorders								
Abdominal discomfort	1 (1)		4 (6)				1 (2)	
Diarrhea			1 (1)					
Dyspepsia			1 (1)		1 (3)			
Nausea			8 (14)		6 (7)		5 (6)	
Vomiting			3 (3)		1 (2)		3 (3)	
General disorders and administration site conditions								
Chest discomfort			1 (1)					
Chills							1 (1)	
Pyrexia	1 (1)							
Investigations								
Alanine aminotransferase increased	2 (2)	1 (1)	4 (4)		2 (2)		3 (3)	
Aspartate aminotransferase increased		1 (1)	1 (1)		2 (2)		2 (2)	
Blood creatine phosphokinase increased		1 (1)		1 (1)				
Red blood cells urine positive	1 (1)	1 (1)	1 (1)					
White blood cell count increased	1 (1)							
Metabolism and nutrition disorders								
Decreased appetite							1 (1)	
Nervous system disorders								
Dizziness							1 (1)	
Headache	1 (1)		2 (2)					
Respiratory, thoracic, and mediastinal disorders								
Epistaxis	1 (1)							
Skin and subcutaneous tissue disorders								
Rash			1 (1)					
Total	4 (8)	2 (4)	11 (35)	1 (1)	8 (16)	—	9 (19)	—

The number of individuals with events (number of events) is shown for each treatment.

In cohort 2, we studied the effect of tegoprazan on the pharmacokinetic variables of triple-antibiotic therapy. The 90% CIs for the geometric mean ratios of metronidazole AUC_{0-6} and $C_{ss,max}$ were within the commonly accepted pharmacokinetic equivalence limit of 0.8−1.25. These observations show that tegoprazan did not alter the pharmacokinetic variables of metronidazole by coadministration. The geometric mean ratios and 90% CIs of AUC_{0-6} and $C_{ss,max}$ were 1.55 (0.99−2.44) and 1.38 (0.72−2.66), respectively, for bismuth. Bismuth showed a high between-subject variability. The exposure of bismuth increased on average in the presence of coadministration with tegoprazan. The results of this study are consistent with those of previous studies which showed that the bioavailability of bismuth could be enhanced by decreased intragastric acidity because the solubility and absorption of bismuth are pH-dependent[21–23]; thus, the blood bismuth concentration reached a high level. When coadministered with omeprazole, the bismuth C_{max} was increased by 2.4 times compared versus that with bismuth alone.[24] Our study showed that the C_{max} (27.86 ng/mL) of bismuth in the steady state after coadministration with tegoprazan was increased by 1.38 times, but it was lower than the bismuth toxicity level of 100 ng/mL.[25] The C_{max} of bismuth in our study was also similar to the C_{max} values of bismuth, 28.08 ng/mL and 30.14 ng/mL, during coadministration with vonoprazan and lansoprazole, respectively, reported in a previous drug interaction study conducted in the Republic of Korea.[1,26] Based on these previous studies, it is expected that the increase in the C_{max} of bismuth when coadministered with tegoprazan would not cause toxic effects.

The AUC_{0-6} and $C_{ss,max}$ of tetracycline were decreased by 38% and 36%, respectively, in the presence of coadministration with tegoprazan. A previous study reported that tetracycline bioavailability was reduced by bismuth subsalicylate.[27] It is hypothesized that the absorption of tetracycline was inhibited by the formation of tetracycline chelate complexes as the solubility of bismuth increased with the coadministration of tegoprazan.[27,28] However, the effect of reduced tetracycline systemic exposure on the clinical efficacy of coadministration of metronidazole, tetracycline, and bismuth with tegoprazan is not believed to be clinically meaningful, as the contribution of systemic, compared with local, antimicrobial activity against *H pylori* has not been established.[29]

In the present study, no serious AEs were reported. The frequency of AEs after coadministration of metronidazole, tetracycline, and bismuth was higher than that after tegoprazan treatment alone. The most frequent AE was nausea. Nausea was reported in all treatment groups except the tegoprazan alone treatment group, and it was predicted to be due to the coadministration of metronidazole, tetracycline, and bismuth. The reported AEs were not significantly different, and there were no clinically significant findings in safety or tolerability when using quadruple therapy, including tegoprazan compared with those when using triple-antibiotic therapy.

This study was conducted only on healthy male subjects. This limitation should be considered to avoid generalizing the results to typical patients, including female patients. Patients might show different pharmacokinetic profiles because of factors such as age, disease progression, or the administration of concomitant drugs. Therefore, further studies in a larger number of patients might be helpful for evaluating the safety and clinical pharmacokinetic characteristics.

CONCLUSIONS

Changes in pharmacokinetic parameters of tegoprazan, tetracycline, and bismuth were detected after concurrent administration. These changes were considered to be mainly due to the pharmacodynamic effect of tegoprazan. There were no significant differences in safety or tolerability when using quadruple therapy, including tegoprazan compared with those when using triple-antibiotic therapy. Therefore, quadruple therapy with tegoprazan instead of a PPI may be proposed for *H pylori* infection treatment.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article. The study sponsor was involved in the study design, collection, analysis, and interpretation.

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