

Effect of meal timing on pharmacokinetics and pharmacodynamics of tegoprazan in healthy male volunteers

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Abstract

Tegoprazan, a novel potassium-competitive acid blocker, is used to treat acid-related diseases. However, there is no information on the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the marketed dosage of tegoprazan under various meal timings in a fed and fasted state. The study aimed to assess the effect of meal timing on PKs and PDs of tegoprazan 50 mg after a single administration in healthy male subjects. An open-label, single-dose, three-treatment, three-period crossover study was conducted. A total of 12 subjects were orally administered a single dose of tegoprazan 50 mg among various conditions: in a fasted state, at 30 min before or 30 min after a high-fat meal. PK parameters were estimated by non-compartmental method. Continuous 24-hour intragastric pH monitoring was done for PD analysis. The PKs and PDs of tegoprazan were compared among the various meal timings. Compared to the fasting condition, the PK profile of tegoprazan was similar when administered 30 min before a high-fat meal; however, delayed absorption with similar systemic exposure was observed when administered 30 min after a high-fat meal. The magnitude of acid suppression evaluated through the PD parameters increased when administered 30 min after a high-fat meal compared to fasting the condition and when administered 30 min before a high-fat meal. However, the increased difference in acid suppression was not clinically significant. Meal timing had no clinically significant effect on the PKs and PDs of tegoprazan 50 mg. Therefore, the marketed dosage of tegoprazan could be administered regardless of the meal timing.

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The authors confirm that the Principal Investigator for this paper was In-Jin Jang MD, PhD and that he had direct clinical responsibility for patients.

Introduction : Tegoprazan, a novel potassium-competitive acid blocker, is used to treat acid-related diseases. However, there is no information on the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the marketed dosage of tegoprazan under various meal timings in a fed and fasted state. The study aimed to assess the effect of meal timing on PKs and PDs of tegoprazan 50 mg after a single administration in healthy male subjects.

Methods : An open-label, single-dose, three-treatment, three-period crossover study was conducted. A total of 12 subjects were orally administered a single dose of tegoprazan 50 mg among various conditions: in a fasted state, at 30 min before or 30 min after a high-fat meal. PK parameters were estimated by non-compartmental method. Continuous 24-hour intragastric pH monitoring was done for PD analysis. The PKs and PDs of tegoprazan were compared among the various meal timings.

Results: Compared to the fasting condition, the PK profile of tegoprazan was similar when administered 30 min before a high-fat meal; however, delayed absorption with similar systemic exposure was observed when administered 30 min after a high-fat meal. The magnitude of acid suppression evaluated through the PD parameters increased when administered 30 min after a high-fat meal compared to fasting the condition and when administered 30 min before a high-fat meal. However, the increased difference in acid suppression was not clinically significant.

Discussion: Meal timing had no clinically significant effect on the PKs and PDs of tegoprazan 50 mg. Therefore, the marketed dosage of tegoprazan could be administered regardless of the meal timing.

What is already known about this subject

- * Tegoprazan, one of the potassium-competitive acid blockers was approved for the treatment of GERD, gastric ulcers and Helicobacter pylori eradication.
- * The systemic exposure of tegoprazan 200 mg between fasting and after meal conditions was comparable, and similar gastric acid suppression was observed.

What this study adds' statements

- * Pharmacokinetic and pharmacodynamic profiles of marketed dosage of tegoprazan under various mealtime conditions which can easily occur in an actual clinical environment was evaluated.
- * There was no clinically significant difference in the pharmacokinetic profiles of tegoprazan 50 mg among fasting or fed conditions.
- * No clinically different efficacy is expected for tegoprazan 50 mg among fasting or fed conditions despite the decreased systemic exposure of active metabolite of tegoprazan in the fed conditions.

Introduction

Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) are common acid-related diseases, and both diseases are generally treated by acid suppression drugs which reduce gastric acid secretion.¹ Among several acid suppression drugs, proton pump inhibitors (PPIs) are most commonly prescribed to treat acid-related diseases over the past several decades.² However, PPIs have several limitations in clinical use due to their own characteristics, including mechanism of action and pharmacokinetics (PKs).

PPIs are converted by acid to active forms which irreversibly inhibit H^+/K^+ ATPase located on the apical membrane of the gastric parietal cell.³ PPIs have relatively short half-lives of about 1 h.⁴ Because of these characteristics, the onset of acid suppression and the recovery after drug cessation are relatively late, and nocturnal acid breakthrough easily occurs even with a twice-daily dosing regimen.⁴⁻⁶

Moreover, noncompliance with PPIs led by a limited administration time is another drawback of PPIs.^{7,8} Considering the mechanism of action requiring acid-activation, it is necessary to intake food when taking

PPIs. However, most PPIs cannot be administered in the fed state due to food effects. According to the previous food effect studies, the bioavailability of esomeprazole is affected by food in that systemic drug exposure is significantly diminished in the fed condition.⁹ In addition, the median % time pH > 4 was 42.0 % when the PPI was administered in the fasting condition; however, it was 17.2 % when administered in the fed condition.¹⁰ Therefore, most PPIs, including omeprazole and lansoprazole, are recommended to be administered about 1 h before meal.¹¹ These limited administration time of most PPIs could trigger treatment failure of acid-related diseases, although some PPIs like dexlansoprazole modified-release formulation can be administered regardless of meal timing.¹²

Recently, potassium-competitive acid blockers (P-CABs) have been developed as novel acid suppression drugs. Tegoprazan, one of the P-CABs was approved for the treatment of GERD, gastric ulcers and *Helicobacter pylori* eradication in South Korea. Tegoprazan has a linear PK profile and dose-dependent pharmacodynamic (PD) profiles in a dose range of 50 to 400 mg, and the time to reach maximum plasma concentration (T_{max}) and the terminal elimination half-life ($t_{1/2}$) of tegoprazan are about 0.5 – 1 h and 3 – 5 h, respectively.¹³ Tegoprazan is mainly metabolized by CYP3A4 to the active metabolite (M1).

The food effect of tegoprazan was already evaluated for 200 mg, and it was verified that tegoprazan had no food effect. The systemic exposure of tegoprazan between fasting and after meal conditions was comparable, and similar gastric acid suppression was observed.¹⁴ Because tegoprazan 200 mg is a higher strength than 50 mg and tegoprazan has a linear PK profile, it is estimated that there is no food effect for tegoprazan 50 mg which is the marketed dosage. However, there is no information on the PK and PD profiles of tegoprazan 50 mg under various mealtime conditions such as ‘administration before a meal,’ which can easily occur in an actual clinical environment. If such profiles are evaluated, the compliance of tegoprazan will improve as the administration time of tegoprazan becomes more clear. Consequently, this study aimed to assess the effect of various meal timings on the PKs, PDs and safety of tegoprazan 50 mg after a single administration in healthy male subjects.

Methods

Subjects and Study Design

The study was reviewed and approved by the Korean Ministry of Food and Drug Safety (MFDS) and the Institutional Review Board of Seoul National University Hospital (clinicaltrials.gov: NCT03863938). This study was conducted at the Seoul National Hospital Clinical Trials Center in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice.

Healthy male volunteers aged between 19 and 50 years with a body mass index of 18.0 to 27.0 kg/m² that were *Helicobacter pylori* negative participated in the study. The health status of the volunteers was determined based on medical history, physical examination, vital sign, 12-lead electrocardiogram (ECG), and clinical laboratory test. Written informed consent was obtained from all the subjects before any study-related procedures.

The study had a randomized, open-label, single-dose, three-treatment, three-period crossover design. In the first period, 24-hour intragastric pH monitoring was conducted as the baseline one day before the administration of tegoprazan. The measurement was started after at least 10 h of fasting, and only lunch and dinner were provided during the measurement. After the baseline monitoring, all the subjects were orally administered a single dose of tegoprazan 50 mg in the fasted state, at 30 min before or at 30 min after a high-fat meal according to the assigned sequence. The high-fat meal contained 900 kcal with over 35 % of fat content, and the subjects were supposed to finish eating within 20 min. After the administration of tegoprazan, 24-hour intragastric pH monitoring for PD assessment and serial blood sampling at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h post-dose for PK analysis of tegoprazan and M1 were conducted. During the intragastric monitoring, the same types of lunch and dinner were provided, and drinking water was prohibited 1 h before and 2 h after the administration of tegoprazan. In the second and third periods, tegoprazan was administered according to the assigned sequence, and the same procedures, including PK/PD assessment, were conducted (Figure 1).

Bioanalytical method

The plasma concentrations of tegoprazan and M1 were measured by a validated method using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) consisting of the ACQUITY UPLC™ System (Waters) and Xevo™ TQ MS (Waters).¹⁵ The validated concentration ranges for tegoprazan and M1 were 20.0 – 10,000 ng/mL and 10.0 – 5,000 ng/mL, respectively. The within-run and between-run precision for tegoprazan was 0.9 – 3.0 % and 1.0 – 2.8 %, respectively. The corresponding values for M1 were 0.8 – 5.6 % and 1.0 – 5.5 %, respectively. The within-run and between-run accuracy was -2.1 – -0.4 % and -3.1 – 1.5 %, respectively, for tegoprazan, and -2.5 – 6.5 % and -3.3 – 1.7 %, respectively, for M1.

Pharmacokinetic assessment

PK parameters were estimated by non-compartmental method using Phoenix WinNonlin® version 8.0 (Certara, St. Louis, MO, USA). The primary PK parameters were maximum plasma concentration (C_{\max}) and area under the concentration–time curve from time zero to the last quantifiable time point (AUC_{last}) of tegoprazan. The secondary PK parameters were T_{\max} and $t_{1/2}$ for tegoprazan, and C_{\max} , AUC_{last} , T_{\max} , $t_{1/2}$, and metabolic ratio (MR) for M1. PK analysis was performed using the concentration-time data collected from the subjects who completed the study without major deviation.

Pharmacodynamic assessment

Continuous 24-hour intragastric pH monitoring was carried out using an ambulatory 24-hour pH recorder, Digitrapper pH 400 (Medtronic, Inc., Fridley, MN, USA) for PD assessment. The PD parameters were evaluated as % time pH [?] 4, mean pH, median pH, and baseline corrected parameters including $\Delta\%$ time pH [?] 4, Δ mean pH and Δ median pH. PD analysis was performed using the collected 24-hour intragastric pH data from the subjects who completed the study and had sufficient pH data over 95% of measuring time.

Safety assessment

Safety was assessed through physical examinations, vital signs, ECGs, clinical laboratory tests and adverse event monitoring.

Statistical analysis

To assess how meal timing affects the PKs of tegoprazan in a fasted state basis, analysis of variance (ANOVA) was conducted with the treatment, period and sequence as the fixed effects and the subject as a random effect. The geometric mean ratios (GMRs) and their corresponding 90 % confidence intervals (CIs) of the C_{\max} and AUC_{last} for 30 min before a high-fat meal to the fasted state and 30 min after a high-fat meal to the fasted state were calculated. To assess the effect of meal timing on PDs, the PD parameters were analyzed with ANOVA in the same manner as the PKs. The statistical analysis was conducted with the SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

Results

1. Study population

A total of 12 subjects were enrolled and randomly assigned to 6 sequences. All of them completed the entire study schedule without any major deviations, so they were included in the PK, PD and safety analysis. The demographics of the subjects were as follows: age, 29.8 ± 4.8 (mean \pm standard deviation) years; height, 174.0 ± 3.3 cm; weight, 71.1 ± 7.9 kg; BMI, 23.5 ± 2.1 kg/m².

Pharmacokinetics

When administered 30 min before a high-fat meal, the PK profile of tegoprazan was similar to the PK profile of tegoprazan when administered in the fasted state (Figure 2 and Figure 3). The C_{\max} of tegoprazan was observed as 775.92 μ g/L and 803.00 μ g/L when administered 30 min before a high-fat meal and in the fasted state, respectively, and the corresponding AUC_{last} was calculated as 2669.82 h[?] μ g/L and 2873.32 h[?] μ g/L,

respectively. The GMRs (90% CIs) for the C_{\max} and AUC_{last} for the 30 min before a high-fat meal to the fasted state were calculated as 0.9631 (0.7517-1.234) and 0.9388 (0.8674-1.016), respectively (Table 1).

When administered 30 min after a high-fat meal, a delayed absorption profile with a decreased C_{\max} and delayed T_{\max} was observed compared with when administered in the fasted state, but the AUC_{last} was similar (Figure 2 and Figure 3). The C_{\max} and AUC_{last} of tegoprazan were calculated as 492.00 $\mu\text{g/L}$ and 3017.05 $\text{h}[\mu\text{g/L}]$, respectively, when administered in the fasted state and 30 min before a high-fat meal. The GMRs (90% CIs) for the C_{\max} and AUC_{last} for 30 min after a high-fat meal to the fasted state were calculated as 0.5396 (0.4211-0.6914) and 1.0455 (0.9661-1.1316), respectively (Table 1).

Compared to the fasted state, the C_{\max} and AUC_{last} of M1 were decreased in both 30 min before and 30 min after a high fat-meal, but MR was similar among the three conditions.

Pharmacodynamics

The profiles of intragastric acidity after tegoprazan administration were similar among the three conditions in that the intragastric pH increased quickly and reached pH 4. However, when administered 30 min after a high-fat meal, the intragastric acidity already reached around pH 4 because of the food neutralized intragastric acid.

Compared to the fasted state, the PD parameters of tegoprazan were similar when administered 30 min before or 30 min after a high-fat meal (Figure 4). The % time pH ≥ 4 was $49.1 \pm 11.6\%$, $53.8 \pm 13.4\%$, and $61.1 \pm 7.6\%$ when administered in the fasted state, 30 min before and 30 min after a high-fat meal, respectively (Table 2). Statistically significant differences of % time pH ≥ 4 , mean pH and median pH were observed by ANOVA test ($p = 0.0018$, $p = 0.0147$, $p = 0.0149$, respectively). As a result of Bonferroni post-hoc, a statistically significant difference in the PD parameters was observed between the conditions when administered in the fasted state and 30 min after a high-fat meal. The adjusted p values were 0.0015, 0.0141 and 0.0127, respectively.

Safety

After the treatment of 30 min before a high-fat meal, two treatment emergent adverse events (TEAEs) occurred (cough and productive cough), and after the treatment of 30 min after a high-fat meal, one TEAE occurred (abdominal pain). The relationships between the TEAE and tegoprazan were assessed as “possible” for abdominal pain and “unlikely” for cough and productive cough. There was no serious adverse event during the entire study. There were no clinically significant findings in the physical examinations, vital signs, ECGs and laboratory tests in all the treatments.

Discussion

This study was conducted to evaluate the PK and PD profiles of the marketed dosage of tegoprazan under various fed conditions compared to the fasting condition. According to the guidelines of Food-Effect Bioavailability and Fed Bioequivalence Studies from the US Food and Drug Administration and MFDS, food effect can be evaluated by comparing the fasted and fed (at 30 min after a high-fat meal) conditions.^{16,17} However, in the actual clinical environment, patients take medicine under various fed conditions, even if they are instructed on when the medicine should be taken. Therefore, in this study, the effect of meal timing was divided into two conditions including before and after meals in order to reflect the actual clinical environment.

In this study, the PK and PD profiles were similar between the fasting and before meal conditions. However, a different PK profile was observed for the after meal condition. The C_{\max} was decreased, and T_{\max} was delayed, while AUC was similar. The result of the reduced C_{\max} and delayed T_{\max} with a similar AUC was in line with a previous food effect study on tegoprazan 200 mg.¹⁴ The phenomenon was possibly caused by physicochemical property of tegoprazan (pH dependent solubility and high permeability) and the delayed time taken by the drug to reach the small intestine where the majority of substances are absorbed. The delayed absorption of the drug tends to occur when taken with food because the volume of the food delays the gastric emptying time so that the drug reaches the small intestine late.^{18,19} However, the AUC repre-

senting the amount of systemic drug exposure of after a meal condition was similar to the other conditions. Considering that the PDs of P-CAB was well correlated to the AUC, there was no clinically significant difference in the PK profiles of tegoprazan 50 mg among the three conditions.²⁰

No clinically different efficacy is expected for tegoprazan 50 mg among fasting or fed conditions despite the decreased systemic exposure of M1 in the fed conditions. M1 has a potency of about one-tenth of its parent compound, and plasma protein binding is about 99 % according to an *in vitro* experiment (unpublished). Considering the molarity calculated based on the C_{\max} basis and the plasma protein binding of M1, the tissue concentration of M1 affecting acid suppression was expected to be negligible. In addition, the total drug exposure calculated by the sum of the AUCs of tegoprazan and M1, taking into consideration of the difference in the potency was comparable among the different fed conditions. Therefore, the difference in M1 among the three conditions did not clinically affect the magnitude of the acid suppression due to the significant difference in the potency.

As expected from the result of the PK, there was no clinically significant difference in PDs of tegoprazan 50 mg among the three conditions. The efficacy of tegoprazan was evaluated by the PD parameters which reflected the change in intragastric pH. Among the various PD parameters, maintaining intragastric pH [?] 4 is representatively used as a clinical threshold for tissue damage and symptoms caused by oesophageal refluxate.^{21,22} In this study, all PD parameters were significantly increased after the administration of tegoprazan regardless of the fasting or fed condition, and the maximum gastric pH was observed as approximately pH 6 which means meal timing did not affect the acid suppression of tegoprazan. However, there was a statistically significant difference in the PD parameters between the fasting and after meal conditions such that increased PD parameters were observed after the meal condition. It is believed that the increased PD parameters are caused by the neutralization of the pH by the food rather than by the drug effect, considering the fasting and after meal condition have a similar AUC and PK-PD relationship.

This study has a limitation in that the baseline intragastric pH measurement was conducted only once at the fasted state in the first period. Considering inconvenience of the subjects during 24-hour intragastric pH monitoring, baselines for the second and third periods with the fed conditions were not measured. Therefore, if further food effect studies are conducted, more accurate results will be obtained if both baselines for the fasting and fed conditions with every period are evaluated.

In conclusion, meal timing had no clinically significant effect on the PK, PD and safety of tegoprazan 50 mg. Therefore, tegoprazan 50 mg is expected to be administered regardless of the meal timing.

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Competing Interests

Naree Shin, Ah Rong Kim, Bong Tae Kim and Geun Seog Song are employees of HK inno.N Corp, Seoul, Korea. All authors declare no conflicts of interest.

Contributors

Deok Yong Yoon, Jung Sunwoo, In-Jin Jang and SeungHwan Lee designed and performed the study and analyzed and interpreted the data. Naree Shin, Ah Rong Kim, Bong Tae Kim and Geun Seog Song were involved in the design of the study and interpretation of the data. SeungHwan Lee takes responsibility for the integrity of the work as a whole, from inception to publishing. All authors reviewed the manuscript and approved the final version of the manuscript for submission.

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