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Original Article

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Enhancing drug administration flexibility: evaluation of pharmacokinetic properties of tegoprazan orally disintegrating tablet (ODT) administered via nasogastric tube or oral dosing

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ABSTRACT

Tegoprazan orally disintegrating tablet (ODT) formulation is a novel formulation to improve a convenience in comparison to taking the conventional tablet of tegoprazan, a potassium-competitive acid blocker. The purpose of this study was to evaluate the pharmacokinetic and safety profiles of tegoprazan ODT when administered via two routes: nasogastric tube or oral dosing. This study is expected to expand the administration route of tegoprazan ODT. The study was conducted in an open-label, randomized, single-dose, two-way crossover design with a 1-week washout period. Healthy subjects aged 19 to 45 years were administered 50 mg of tegoprazan ODT orally or dissolved in water via nasogastric tube. Tegoprazan, the active ingredient, was quantified using a ultra-high performance liquid chromatography tandem mass spectroscopy (UPLC-MS/MS), and pharmacokinetic parameters were determined through non-compartmental analysis. Safety was monitored throughout the study. A total of 48 subjects, successfully completed the trial. The geometric mean ratios for log-transformed C_{max} and AUC_t, representing the ratio of nasogastric tube group to oral dosing group, along with 90% confidence intervals, were 1.1087 (1.0243–1.2000) and 1.0023 (0.9620–1.0442), respectively. All adverse events were unrelated to tegoprazan and mild in intensity. The pharmacokinetic profiles of tegoprazan ODT were equivalent between the nasogastric tube and oral administration. Considering the demonstrated linear pharmacokinetics and concentration-dependent pharmacodynamics of tegoprazan, the administration via nasogastric tube is expected to yield effects equivalent to those of oral administration. This approach offers a viable alternative, especially beneficial for patients with oral intake difficulties.

Keywords: Potassium-Competitive Acid Blocker; Orally Disintegrated Tablets (ODT); Nasogastric Tube; Pharmacokinetics

Author Contributions

Conceptualization: Ghim JL; Data curation: Oh M; Formal analysis: Oh M; Investigation: Cho YS; Methodology: Choi YK; Visualization: Choi YK; Writing - original draft: Kim HS; Writing - review & editing: Kim HS, Ghim JL.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a prevalent chronic upper gastrointestinal disease that manifests as stomach contents and acid refluxing into the esophagus, leading to symptoms like chest pain or nausea [1]. A meta-analysis reported a worldwide pooled prevalence of symptoms occurring at least once a week, approximately 13%, with significant geographical variation-from rates exceeding 25% in South Asia to less than 10% in Canada and France [2]. This variation highlights the global burden of GERD and underscores the necessity for effective management strategies tailored to diverse populations.

According to a recent clinical guideline [3], the management of GERD involves multifaceted approaches including lifestyle modifications, pharmacological intervention such as proton pump inhibitors (PPIs), and surgical options for those unresponsive to medicine. In some regions like Korea, a clinical guideline recommends potassium-competitive acid blockers (P-CABs) as an alternative to PPIs due to their comparable effectiveness [4]. P-CABs, including tegoprazan developed by HK inno.N corp. (Seoul, Korea), target the same hydrogen-potassium adenosine triphosphatase (H+-K+ ATPase) pump as PPIs but are acid-stable and reversibly bind to the proton pump. This allows for more flexible dosing schedules and potentially quicker therapeutic effects [3,5,6].

Tegoprazan is particularly noted for its rapid, potent, and sustained acid suppression, making it a valuable option for patients with GERD, gastric ulcers, and in the management of *Helicobacter pylori* infections. Its approval and use in countries such as the Korea and China mark it as a significant advancement in GERD treatment [7].

Transitioning to the issue of dysphagia—a condition characterized by difficulty swallowing—this symptom is notably prevalent among older adults and those with severe GERD, affecting 8–22% of adults aged over 50 years [8]. Dysphagia not only complicates the administration of oral medications but also significantly impacts nutritional status and quality of life. Enteral nutrition via tube feeding, often favoured over parenteral alternatives, highlights the need for medication forms that can be administered effectively under such conditions [9].

Thus, the introduction of tegoprazan as an orally disintegrating tablet (ODT) presents a promising alternative. These tablets dissolve quickly without water, offering an advantageous option for patients who struggle with swallowing or where water is scarce. This study aims to evaluate the pharmacokinetics and safety of tegoprazan ODT administered via nasogastric tube compared to oral administration, exploring a potential new route that may benefit a broader range of patients, particularly those who require nasogastric tube feeding.

METHODS

Subjects

The study protocol, including all amendments, was approved by the Institutional Review Board (IRB) of Inje University Busan Paik Hospital (IRB approval number: 2023-04-005) and the Korea Ministry of Food and Drug Safety. The study was conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All participants were fully informed about the risks and benefits of participation and provided their written, signed, and dated informed consent voluntarily before participating in the clinical trial.

Eligible participants were healthy males aged 19–45 years with a body mass index (BMI) of 18.5–28.0 kg/m^2.

Exclusion criteria were as follows: any history or evidence of hepatic, renal, gastrointestinal, pulmonary, musculoskeletal, endocrine, psychiatric, hemato-oncologic, urinary, or cardiovascular disorders; conditions preventing nasogastric tube insertion; abnormal baseline laboratory test results including alanine aminotransferase or aspartate aminotransferase levels greater than 1.5 times the upper limit of normal; total bilirubin levels exceeding twice the upper limit of normal; any clinically relevant abnormalities on electrocardiogram (ECG); positive drug screening results; known drug allergies; history of drug abuse; current use of any medication that could affect the absorption, distribution, metabolism, or excretion of the study drug; consumption of any medication within 10 days prior to the screening visit; participation in another investigational drug study within the previous 6 months; donation of whole blood within 60 days prior to the screening visit; inability to use medically acceptable methods of contraception; alcohol consumption exceeding 30 g per day; smoking more than 10 cigarettes per day; or caffeine intake exceeding 400 mg per day.

Study design

This study was conducted as a randomized, open-label, two-way crossover study with a 1-week washout period between treatments. Each subject received a single 50 mg dose of tegoprazan ODT (K-CAB ODT Tab, HK inno.N Corp., Seoul, Korea) either orally or via a nasogastric tube. The dose and washout period were based on prior studies of tegoprazan ODT, which demonstrated a T_{max} of approximately 0.75 hours and a $t_{1/2}$ of around 4.5 hours, with rapid disintegration time of the ODT format of less than 30 seconds, ensuring minimal impact on the absorption rate differences between administration routes [10].

Participants were randomly assigned to one of two administration sequence groups—oral followed by nasogastric tube, or vice versa—using a SAS-generated random number table. Subjects were admitted to the clinical trial center the day before drug administration, provided with a standard dinner, and then fasted for at least 10 hours prior to dosing.

On the morning of study day 1, under supervisory conditions, each subject received the study drug according to their assigned sequence. Subjects either took the 50 mg dose of tegoprazan ODT with 110 mL of water orally or via a nasogastric tube setup. For the nasogastric tube administration, the nasogastric tube was inserted by experienced investigators. The successful placement of nasogastric tube was confirmed by the whoosh test, which involves rapidly injecting air down the nasogastric tube while auscultating for a whooshing sound over the epigastrium [11]. And then the drug was prepared as follows (**Fig. 1**). The tablet was placed in 10 mL of water in a 50 mL syringe and allowed to dissolve without agitation, ensuring the integrity of the solution. The dissolved medication was then administered through a 16-French Levin-type nasogastric tube. This was followed by flushing the tube with 20 mL of water, repeated four times to ensure complete delivery. In compliance with the crossover design, subjects switched the route of administration after a 1-week washout period for the subsequent dosing session. All participants maintained a sitting posture for at least 4 hours post-dose to facilitate gastric emptying. Standardized meals were provided 4 and 10 hours after dosing.

Safety evaluations were conducted, and subjects were discharged on Day 2. Blood samples were collected at predefined time points (0, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post-dose) for pharmacokinetic analysis. After a 1-week washout period, subjects

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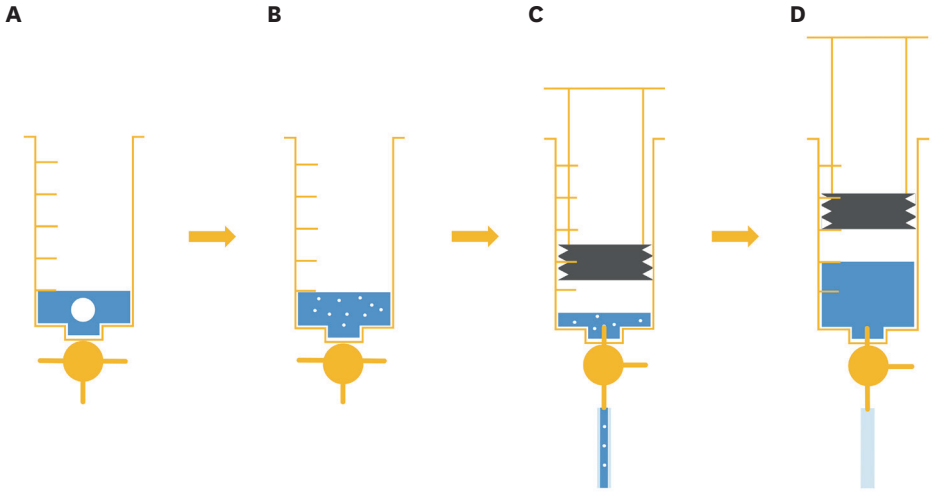

Figure 1. Administration method of tegoprazan ODT via nasogastric tube. The tegoprazan 50mg ODT was placed in 10 mL of water in a 50 mL syringe (A) and then disintegrated for a few seconds without shaking (B). The tegoprazan dissolved solution was administered through a 16-French Levin-type nasogastric tube inserted into the subjects (C). The syringe was flushed with 20 mL of water, repeated four times to ensure complete delivery (D).
ODT, orally disintegrating tablet.

underwent the alternative administration. Plasma samples were immediately stored at −80°C to −60°C and shipped on dry ice to BioInfra Co. Ltd. (Korea) for analysis.

Bioanalysis

Plasma concentrations of tegoprazan were measured using a validated method involving ultra-high-performance liquid chromatography (UPLC) coupled with tandem mass spectrometry (MS/MS). Specifically, the analysis was performed using the Waters ACQUITY UPLC™ System (Waters, Milford, MA, USA) equipped with a Waters Xevo™ TQ-S MS detector. Tegoprazan samples were extracted from human plasma via a liquid-liquid extraction method using a mixture of methanol, water, and formic acid (30/70/0.1, v/v/v). Following extraction, tegoprazan-d6, used as the internal standard, was added.

The extracted samples were injected onto a Waters ACQUITY UPLC® BEH C18 column (1.7 µm, 2.1 mm ID × 50 mm L), protected by a Waters ACQUITY UPLC™ Column In-Line Filter. The mobile phase consisted of 0.1% (v/v) formic acid in both distilled water and methanol, delivered at a flow rate of 0.3 mL/min. Detection was carried out in the positive ion electrospray mode using multiple reaction monitoring. The monitored ion transitions were m/z 388.20 to 220.26 for tegoprazan and m/z 394.22 to 226.32 for tegoprazan-d6.

A calibration curve was established over a range of 20–10,000 ng/mL. Both intra-day and inter-day coefficients of variation were maintained below 15%, and the accuracy was greater than 96%. No significant crosstalk or matrix effects were observed.

Safety assessment

Adverse events (AEs) were systematically monitored throughout the study. This monitoring involved scheduled physical examinations and specific inquiries about general health-related issues posed to the subjects. Clinical laboratory tests, vital signs assessments, physical examinations, and 12-lead ECGs were conducted at scheduled time points from the day before dosing until the time of discharge.

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All abnormalities that were clinically significant were meticulously recorded as AEs. The investigators evaluated these events in terms of their severity, progression, outcome, seriousness, and potential relationship to the study drug. This comprehensive evaluation included all AEs, regardless of their suspected association with the study medication.

Pharmacokinetic data analysis

The pharmacokinetic parameters of tegoprazan were determined using Phoenix WinNonlin® software version 8.3 (Certara USA, Inc., Princeton, NJ, USA). The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were derived directly from the plasma concentration-time curves. The area under the plasma concentration-time curve from zero to last observation (AUC_t) was calculated using the linear trapezoidal method.

The terminal elimination half-life ($t_{1/2\beta}$) was estimated by dividing ln (2) by the terminal phase rate constant (λz), which is associated with the terminal (log-linear) portion of the curve. Oral clearance (CL/F) was calculated by dividing the dose by AUC from time zero to infinity ($AUC_{0-\infty}$). The apparent volume of distribution (Vd/F) was determined by dividing CL/F by λz.

Statistical analysis

The sample size calculation was based on an intrasubject coefficient of variation (CV%) of 25.78% for C_{max} (the pharmacokinetic parameter with the highest variability) from a previous study. Assuming conservatively a mean difference in C_{max} of log0.925, at a 5% significance level (α) and with 80% statistical power (1-β), the required number of subjects was calculated to be 40. To account for a possible dropout rate of 15%, the final sample size was set at 48 participants.

Pharmacokinetic data analyses were conducted using data from subjects who completed the study, while safety evaluations utilized data from all participants who received the study drug. Descriptive statistics summarized demographic characteristics, safety data, and PK parameters. Equivalence between the nasogastric tube and oral administration routes was tested using two one-sided tests at a significance level of $\alpha = 0.05$. The study was considered to demonstrate bioequivalence if the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) for C_{max} and AUC_t fell within the range of 0.80–1.25.

The frequency of AEs between the two administration routes was compared using Fisher's exact test. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subjects

A total of 52 male subjects were initially enrolled and randomized in the study. Due to failures in nasogastric tube insertion among other reasons, four participants dropped out of the study. They were replaced by reserve candidates, ensuring that 48 subjects successfully completed the clinical trial. The pharmacokinetic analysis included data from these 48 subjects, while safety assessments were conducted on the data from the 50 subjects who received at least one dose of the study drug.

The ranges of heights and weights of the enrolled subjects were 164.3–194.4 cm and 50.5–93.9 kg, respectively. In terms of demographic characteristics for pharmacokinetic sets, the

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subjects in the oral-first sequence group (RT) had slightly higher average weight, height, and BMI compared to those in the nasogastric tube -first sequence group (TR). Specifically, the RT group had an average age of 28.38 years (± 5.32), weight of 79.18 kg (± 10.27), height of 178.43 cm (± 6.68), and BMI of 24.79 kg/m^2 (± 2.74). In contrast, the TR group recorded an average age of 28.29 years (± 6.08), weight of 70.38 kg (± 10.55), height of 173.88 cm (± 5.17), and BMI of 23.15 kg/m^2 (± 2.83).

Pharmacokinetics

The mean plasma concentration-time profiles of tegoprazan are depicted in **Fig. 2**, with descriptive statistics for the pharmacokinetic parameters presented in **Table 1**. The profiles were visually similar for both oral and nasogastric tube administration. Tegoprazan was rapidly absorbed when administered orally or via nasogastric tube, with a median T_{max} of approximately 0.75 hours and 0.5 hours, respectively. It was also rapidly eliminated, with a terminal half-life ($t_{1/2\beta}$) of approximately 4.4 hours for oral administration and 4.3 hours for nasogastric administration. The absorption of tegoprazan following nasogastric tube administration tended to be slightly faster compared to oral administration.

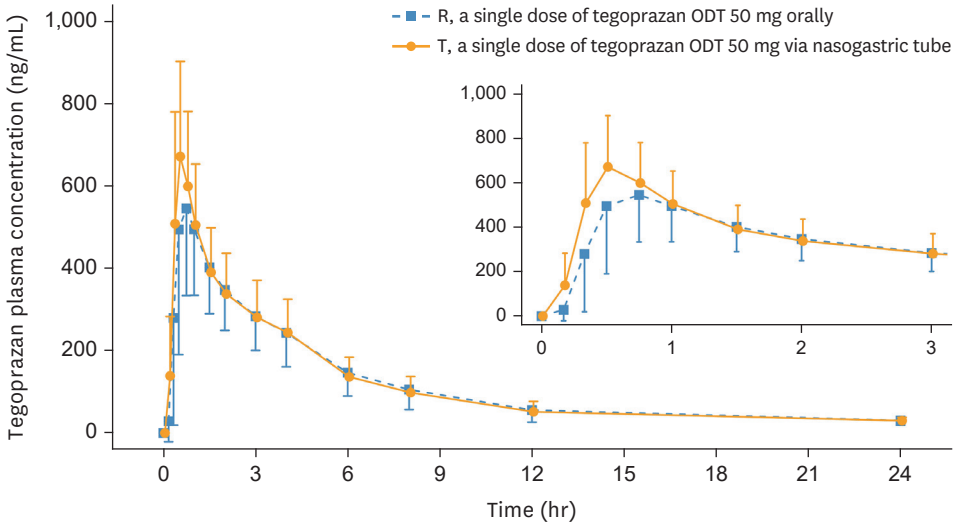

Figure 2. Plasma concentration-time profiles of tegoprazan after administration of tegoprazan 50 mg ODT orally or via nasogastric tube in 48 healthy male subjects.
ODT, orally disintegrating tablet.

Table 1. Pharmacokinetic parameters of tegoprazan after administration of 50 mg tegoprazan orally disintegrating tablet via orally or nasogastric tube in 48 healthy male subjects

Parameters	Orally (n = 48)	Nasogastric tube (n = 48)
C_{max} (ng/mL)	650.44 ± 217.62 (33.46%)	716.27 ± 217.31 (30.34%)
AUC_t (hr*ng/mL)	2,508.40 ± 1,064.93 (42.45%)	2,482.56 ± 968.81 (39.02%)
$AUC_{0-\infty}$ (hr*ng/mL)	2,746.31 ± 1,130.26 (41.16%)	2,720.98 ± 1,029.41 (37.83%)
$AUC_{extrapolation}$ (%)	9.00 ± 2.98 (33.13%)	9.02 ± 2.76 (30.64%)
T_{max} (h)*	0.75 (0.33–3.00)	0.50 (0.33–1.00)
$t_{1/2\beta}$ (h)	4.42 ± 1.35 (30.51%)	4.27 ± 1.30 (30.50%)
CL/F (L/h)	21.02 ± 7.79 (37.08%)	20.77 ± 7.26 (34.98%)
Vd/F (L)	122.72 ± 26.57 (21.65%)	118.66 ± 26.26 (22.13%)

C_{max}, the maximum plasma concentration; AUC_t, the area under the plasma concentration-time curve (AUC) from zero to last observation; $AUC_{0-\infty}$, the AUC from zero to infinity; $AUC_{extrapolation}$, the percentage of AUC obtained by extrapolation; T_{max}, the time to reach C_{max}; $t_{1/2\beta}$, the terminal elimination half-life.
Data are expressed as arithmetic mean ± standard deviation (coefficient variation, %).
*Values expressed as median (range).

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Table 2. Statistical assessment of bioequivalence of tegoprazan after administration of 50 mg tegoprazan orally disintegrating tablet via orally or nasogastric tube

Parameters	Orally	Nasogastric tube	Geometric mean ratio (90% CI)
C_{max}	614.09	680.82	1.1087 (1.0243–1.2000)
AUC_t	2,318.51	2,323.79	1.0023 (0.9620–1.0442)

C_{max}, the maximum plasma concentration; AUC_t, the area under the plasma concentration-time curve (AUC) from zero to last observation; CI, confidence interval.
Data are expressed as geometric mean.

No clinically significant differences in pharmacokinetic parameters were observed between the two administration routes. The geometric mean ratios (GMRs) of C_{max} and AUC_t for tegoprazan (nasogastric tube vs. oral administration) were 1.1087 (90% CI: 1.0243–1.2000) and 1.0023 (90% CI: 0.9620–1.0442), respectively, as shown in **Table 2**. The 90% CIs of the GMRs for both C_{max} and AUC_t were within the accepted bioequivalence range of 0.80–1.25.

Safety

AEs occurred in 3 of the 50 subjects who received the study drug. These included vomiting related to nasogastric tube insertion, transiently elevated AST levels attributed to excessive exercise before administration of tegoprazan, and minor bleeding at a catheter insertion site. Subjects who vomited were deemed unsuitable for pharmacokinetic evaluation and were consequently dropped out of the study. All affected subjects recovered without any treatment or sequelae. Each AE was classified as mild and not directly associated with the drug, indicating good tolerability of tegoprazan ODT. No significant differences were observed in the frequency or severity of AEs between the oral and nasogastric tube administration routes ($p > 0.05$).

DISCUSSION

This study was designed to evaluate the pharmacokinetics and safety of tegoprazan ODT, administered in a 50 mg dosage both orally and via nasogastric tube, in healthy male subjects. Our findings confirmed bioequivalence between the two administration routes with no clinically significant differences in AEs, supporting the use of nasogastric tube delivery for patients unable to take oral medications.

Nasogastric tube administration is often necessary for patients with severe dysphagia, traumatic medical events, or neurological disorders [12]. Traditional PPIs can also be administered through a nasogastric tube but often present challenges such as the need for tablets to be shaken for more than 2 minutes to disintegrate and the immediate administration of granules from capsules to prevent tube blockage [13]. Unlike some PPIs, which have shown high variability when administered via nasogastric tube due to adherence of the medication to the tube, tegoprazan ODT disintegrates within seconds without the need for shaking and does not block the tube, offering a significant advantage in terms of convenience and reliability [14,15].

Furthermore, the pharmacokinetic variability of tegoprazan ODT when administered via nasogastric tube is comparable to that of oral administration (30% vs. 33% for C_{max} and 39% vs. 42% for AUC_t). This suggests that tegoprazan ODT can provide consistent drug effects, making it a beneficial option for patients requiring gastric acid suppression via nasogastric feeding.

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Considering the long-term use of the nasogastric tube [16], a multiple-dose study of tegoprazan ODT via nasogastric tube may be needed to evaluate the pharmacokinetics and safety of tegoprazan. Previous multiple-dose studies of tegoprazan have reported no drug accumulation and no significant differences in safety between single and multiple doses [17-19]. Therefore, it is expected that there will be no significant differences in the pharmacokinetics and safety of tegoprazan after multiple doses via nasogastric tube.

In summary, the pharmacokinetic profiles of tegoprazan ODT were equivalent between the nasogastric tube and oral administration. Considering the demonstrated linear pharmacokinetics and concentration-dependent pharmacodynamics of tegoprazan, the administration via nasogastric tube is expected to yield effects equivalent to those of oral administration. This approach offers a viable alternative, especially beneficial for patients with oral intake difficulties.

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