Bioavailability and Tolerability of Combination Treatment With Revaprazan 200 mg + Itopride 150 mg: A Randomized Crossover Study in Healthy Male Korean Volunteers

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ABSTRACT

Background: To date, no definitive treatment of functional dyspepsia (FD) has been proven to be effective and reasonably well-tolerated. Proton pump inhibitors (PPIs) combined with prokinetic agents are considered an effective option. Revaprazan is a selective potassium-competitive acid blocker that reversibly inhibits gastric H^+/K^+-ATPase and shows effective acid suppression comparable to PPIs. Itopride is a prokinetic agent that has anticholinesterase activity as well as dopamine D_2 receptor antagonistic activity. For this reason, revaprazan and itopride have been prescribed for FD; however, no available studies have reported the pharmacokinetic interactions of these 2 drugs.

Objective: The objective of this study was to compare the bioavailability and tolerability of revaprazan and itopride combination therapy to those of equally dosed monotherapies to acquire basic drug–drug interaction information about revaprazan.

Methods: This multiple-dose, randomized crossover study was conducted in healthy male Korean subjects. Subjects received, in randomized sequence, a 7-day oral dose of revaprazan 200 mg once daily, itopride 50 mg TID, or both. Each treatment period was separated by a 7-day washout period. Blood samples were collected for up to 24 hours following the last dose at steady state, and drug concentrations were determined using validated LC/MS-MS. Pharmacokinetic properties were obtained using noncompartmental analysis. Drug tolerability was assessed throughout the study, using measurements of vital signs, clinical chemistry testing, and interviews.

Results: A total of 30 subjects were enrolled in the study. Among them, 28 subjects completed revaprazan treatment, and 27 completed the study (3 subjects were withdrawn). The geometric mean ratios (GMRs) (90% CI) of $C_{max,ss}$, and $AUC_{\tau,ss}$ with revaprazan were 0.92 (0.84–1.00) and 0.96 (0.89–1.03), respectively. The GMRs of $C_{max,ss}$ and $AUC_{\tau,ss}$ with itopride were 1.07 (0.96–1.20) and 1.12 (1.06–1.18), respectively. A total of 15 adverse events (AEs) were reported in 8 subjects. All AEs were considered to be mild, and there were no clinically significant differences between treatment groups.

Conclusion: The findings from this study suggest bioequivalence between revaprazan given as monotherapy and in combination with itopride in these healthy Korean male volunteers, with no clinical significant drug–drug interaction. All treatments in this study was generally well tolerated. ClinicalTrials.gov identifier: NCT0133289. (*Clin Ther*. 2012;34:1999–2010)

Key words: combination therapy, healthy subjects, itopride, pharmacokinetics, revaprazan.

INTRODUCTION

Functional dyspepsia (FD) is a common morbid condition characterized by pain and/or discomfort in the upper abdominal area. It has a reported prevalence rate between 20% and 40% in developed countries.[1] According to the Rome III criteria for FD,[2] patients must have ≥6-month history of ≥1 of the following symptoms: bothersome postprandial fullness, early satiation, and epigastric pain or burning, each lasting ≥3 months. Although peptic ulcer disease, gastroesophageal reflux disease, biliary tract disease, or gastric can-

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cer are be found in up to 40% of patients with dyspepsia, the majority of these cases are finally diagnosed as FD. Because of the high prevalence of FD and the absence of a definitive treatment, the disease is regarded as a major clinical problem worldwide. Several clinical trials have been carried out to improve the management of FD, but because of a lack of proper biomarkers to describe symptoms and the difficulty of validating outcomes measures, some trials have reported unsatisfactory results. In addition, some patients do not respond to the various treatment options.[3–5] Recently, FD was subclassified into 2 syndromes: postprandial distress syndrome and epigastric pain syndrome.[6,7] So, more suitable treatments based on predominant symptoms relevant to FD syndrome subtype are being considered.[2,8,9]

Some clinical trials have reported the effectiveness proton pump inhibitors (PPIs) in the treatment of acid-related diseases.[10–13] PPIs may help to alleviate the symptoms of FD by suppressing gastric acid, which plays an important role in causing the symptoms of dyspeptia.[14–18]

In addition, it is believed that impaired gastric accommodation contributes to the pathophysiology of postprandial distress syndrome.[19–21] Prokinetic agents are drugs that stimulate gastric emptying by increasing contractions of smooth muscles in the stomach, as well as modulating visceral hypersensitivity. They have been considered an effective treatment of upper gastrointestinal motor disorders.[22–24] Therefore, several patients have recently been given PPIs in combination with prokinetic agents to control FD symptoms.[25–27]

Revaprazan is a first-in-class potassium–competitive acid blocker (P-CAB), which bind reversibly to proton pumps and act by competing with K^+ on the H^+/K^+-ATPase enzyme.[28] In contrast to PPIs, which irreversibly suppress the H^+/K^+-ATPase enzyme, revaprazan may inhibit gastric acid secretion effectively without hypergastrinemia.[29] Clinical trials have reported that revaprazan effectively inhibits acid secretion.[28–30] Therefore, compared with conventional PPIs, revaprazan may provide more effective symptom control for FD. Itopride, a benzamide derivative, dopamine D_2 receptor antagonist, and acetylcholinesterase inhibitor, has been used as a prokinetic agent in the treatment of FD.[31,32] A recent placebo-controlled trial of itopride in patients with FD reported a significant improvement in symptoms.[33] Because of these findings, revaprazan and itopride combination therapy has been prescribed for the treatment of FD, although no study has yet evaluated the pharmacokinetic interactions between the 2 drugs.[34]

The present study compared the tolerability and pharmacokinetic properties of revaprazan and itopride administered as monotherapy and in combination in healthy male Korean subjects to assess the drug–drug interaction data for the marketing of revaprazan.

SUBJECTS AND METHODS

Inclusion and Exclusion Criteria

Male Korean volunteers between 20 and 50 years of age were enrolled in the present study. Each was in good health, as determined using medical history, physical examination, vital sign measurements, ECG, and laboratory testing. Laboratory testing included complete blood cell count, blood chemistry, and urinalysis and were performed at the Department of Laboratory Medicine of the Asan Medical Center (Seoul, Korea), accredited by the Korean Association of Quality Assurance for Clinical Laboratories and certified by the College of American Pathologists. Subjects had a body mass index between 19 and 27 kg/m^2 and were negative for HIV antibody, hepatitis B surface antigen, hepatitis C virus, and syphilis high-quality regain test.

Subjects were excluded if they had any of the following: use of any prescription drug or over-the-counter medication within 14 or 7 days, respectively, before the start of the trial; blood donation in the 60-day period prior to drug administration; a history or clinical evidence of a clinically significant gastrointestinal disorder, such as gastric ulcer or gastroesophageal reflux disease; and/or a history of clinically significant drug allergy to revaprazan or itopride. Participants were prohibited from using xanthine-containing beverages, nicotine, and herbal products/drugs for the period beginning 7 days before the first administration of the study drug and ending on the last day of the study period.

All subjects were informed of the study by the clinical investigators and provided written informed consent prior to screening examination procedures. The trial was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki.[35,36] The institutional review board at Asan Medical Center approved the protocol prior to the start of the study.

Study Design

In this multiple-dose, randomized, open-label crossover study, subjects began the first of 3 treatment periods by being randomly allocated in a 1:1:1:1:1:1 ratio, to 1 of 6 treatment sequences (ABC, CAB, BCA, CBA, BAC, or ACB) before the initiation of the study, using a randomization table. The randomization code was generated using R version 2.10.1 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). Each envelope for a given (numbered) subject concealed the subject's matched treatment sequence until administration. The sequence determined the order in which subjects received treatments. Treatment A was revaprazan 200 mg once daily; treatment B was itopride 50 mg TID; and treatment C was coadministration of revaprazan 200 mg once daily + itopride 50 mg TID. Each treatment was administered for 7 days, with a 7-day washout period in between.

All subjects visited the hospital for 5 consecutive days for study drug administration. At regular time intervals (0, 24, 48, 72, and 96 hours) after an overnight fast, the drug(s) were taken with 240 mL of plain water, after which subjects were allowed to return home. They could eat breakfast ≥30 minutes after dosing. During treatment periods B and C, subjects received 2 additional pills of itopride each day, to be taken at home in the afternoon and evening. They were given a medication diary in which they were asked to record the exact time at which they took the drug. Lunch and dinner could be consumed only after 30 minutes from dosing, and they could not eat any food before until ≥2 hours after dosing. On days 1 and 5, blood samples were taken from all subjects before the drugs were received.

From days 6 to 8, subjects were admitted to the hospital. On day 6, they received treatment following the standard protocol. In the morning of day 7, they were given the last pill(s), and blood samples were taken up to 24 hours from the last administration. All subjects were discharged on day 8. After the washout period, subjects repeated the protocol during the next time period, according to the prearranged treatment sequence.

Blood Sample Collection

Blood samples (8 mL) were collected for drug concentration analysis at 0 hours (on day 1) and 96 hours (on day 5) on an outpatient basis. After hospital admission, 120-hour (day-6) and 144-hour (day-7) samples were collected before each drug administration. After the last drug administration, blood samples were taken at 144.25, 144.5, 144.75, 145, 146, 147, 148, 150, 152, 156, and 158 hours. All blood samples were collected by an indwelling catheter inserted into a forearm vein, except at 0 and 96 hours (outpatient basis sampling process) when samples were collected using direct venipuncture. Samples were collected into heparinized tubes, and 1 mL of blood was discarded when obtained from the inserted catheter. To maintain patency, 1.5 mL of normal saline was injected into the catheter after each blood sample was drawn. All samples were put immediately on ice, and within 40 minutes of collection, plasma was extracted using centrifugation at 1800*g* at 4°C for 8 minutes and immediately transferred to Eppendorf tubes (1.5 mL) that were frozen at −70°C. These were packed in dry ice to maintain the temperature at <–50°C for transportation to the central laboratory (International Scientific Standard Corporation, Chuncheon, Korea, certified by GLP [Good Laboratory Practice] of the Korea Food and Drug Administration [KFDA]), where they were analyzed.

Statistical Analysis

Plasma concentrations of revaprazan and itopride were measured separately by International Scientific Standard Corporation. The method used at the International Scientific Standard Corporation was validated according to standard operating procedures and KFDA guidelines on bioanalytical method validation, based on FDA guidance.[37] The plasma concentrations of drugs were determined using validated high-performance LC/MS-MS (Shimadzu Corporation, Kyoto, Japan) using known methods.[29,38] Revaprazan, itopride, and the internal standard (IS) solutions (mosapride) were provided by Yuhan Corporation, Seoul, Korea. The HPLC system was coupled with the API 5000 MS/MS detector (Applied Biosystems Inc, Foster City, California). Chromatographic separation was achieved on a 150 × 2.1-mm, 5-μm internal-diameter hypersil gold column. The mobile phase consisted of 10-mM ammonium acetate:acetonitrile (20:80 vol/vol, containing 0.1% formic acid) at a flow rate of 0.30 mL/min. Mass spectrometry equipped with a Turbo ion spray interface was run in ESI (Electrospray ionization) mode, and the ion source temperature was set at 500°C, with ultra–

high-purity nitrogen as the collision gas. Ion spray voltage was set at 4500 V.

Briefly, revaprazan and itopride standard solutions were dissolved in acetonitrile and methanol, respectively, and diluted in blank serum to provide concentrations of 10, 30, 50, 100, 500, 1000, and 2000 ng/mL. Then, 20-μL IS solution (mosapride 3 μg/mL), 50 μL 1N NaOH, and 1-mL MTBE was added to 100 μL of all standard samples. The mixture was thoroughly vortexed at 0.9*g* for 15 minutes and centrifuged at 11147*g* for 5 minutes, followed by deep-freezing at −80°C for 20 minutes. Supernatants were evaporated under 45°C N_2, and redissolved in 10-mM ammonium acetate:acetonitrile (20:80 vol/vol) solution, and 5 μL was injected into the high-performance LC-MS/MS system. The calibration standards and blanks were freshly prepared for each assay and were extracted along with serum and quality-control (QC) samples.

The validation scheme covered the analysis of calibration curves and QC samples at different concentrations to determine selectivity, linearity, intra- and interassay precision, accuracy, stability, and recovery. No significant chromatographic interference was observed between revaprazan and itopride at the retention times for blank plasma. The retention periods were 1.9 and 1.5 minutes for revaprazan and IS, respectively, and 1.3 and 1.5 minutes for itopride and IS, respectively.

Drug-to-IS peak area ratios for revaprazan and itopride standards were used to create linear calibration curves using $1/\chi^2$ weighted least-squares regression analysis. Calibration curves were linear over the range 10 to 2000 ng/mL for both drugs. The lower limit of quantification was 10 ng/mL for each. A calibration curve for revaprazan, gradient b was ~0.00112 to 0.00122, while a curve for itopride, gradient b was

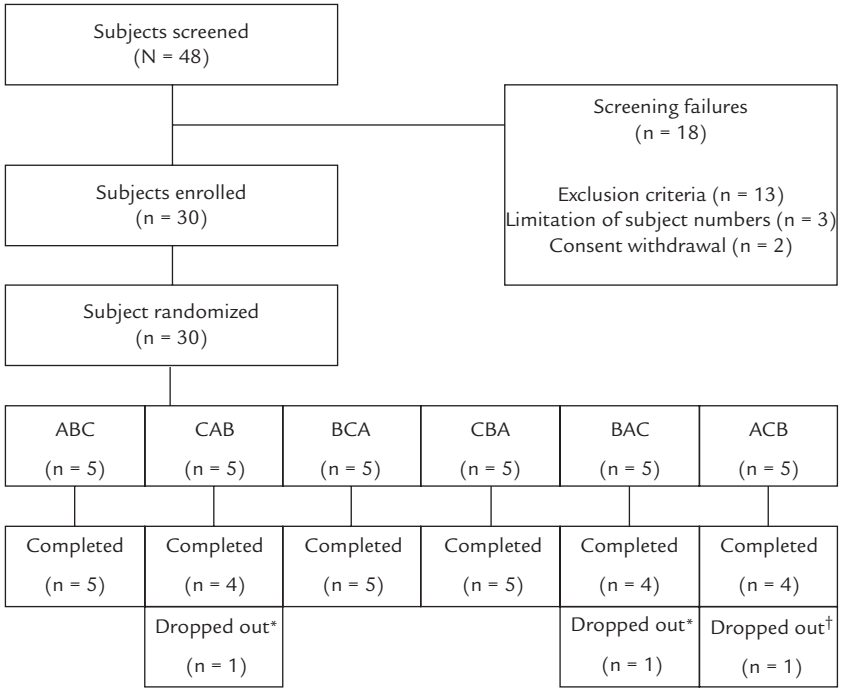

Figure 1. Disposition of the healthy Korean subjects in this study of the tolerability and pharmacokinetic properties of revaprazan 200 mg and itopride 150 mg administered as monotherapy and in combination. Treatment A was a 7-day oral dose of revaprazan 200 mg monotherapy; treatment B was a 7-day oral dose of itopride 50-mg TID monotherapy; treatment C was a 7-day coadministration of revaprazan 200 mg once daily + itopride 50 mg TID. In each group, 5 subjects received predetermined study drugs. *Two subjects withdrew consent after completing the second period. †One subject withdrew consent after completing the first period.

~0.00086 to 0.00089. For all calibration curves, the R^2 value was always >0.99.

QC samples were used to evaluate intra- and interassay precision and accuracy. They were prepared by spiking human serum with 10, 30, 1000, and 1600 ng/mL of revaprazan or itopride. For revaprazan, intraday precision, expressed as % CV, ranged from 2.1% to 4.7%, and interday precision ranged from 5.9% to 9.2%. For itopride, intraday precision ranged from 1.5% to 7.5%, and interday precision ranged from 2.2% to 6.2%. The intraday accuracy for revaprazan ranged from 99.2% to 105.1%, and the interday accuracy ranged from 97.3% to 99.4%. For itopride, the intraday accuracy was between 97.6% and 110.6%, and the interday accuracy was between 98.0% and 100%.

Tolerability Assessments

To evaluate tolerability, subjects who received ≥1 dose of drug were observed for adverse events (AEs). Tolerability assessments included the regular monitoring and recording of all AEs and any concurrent medications or significant nondrug therapies. The AEs were described using time of occurrence, time of end, intensity, relations of clinical drug, result, and any treatment action taken. All AEs were evaluated and recorded by unmasked investigators throughout the study.

Evaluation of routine blood chemistry, blood counts with white cell differential, urine analyses, as well as a physical examination, ECG, and monitoring of vital signs, were performed at regular intervals. Vital signs including blood pressure and heart rate were measured with the subject in a sitting position and using an automated device (Vital Signs Monitor 300 series, Welch Allyn Inc, Skaneateles Falls, New York), and body temperature was measured with a tympanic thermometer (Braun Thermoscan, Kaz USA, Inc, Southborough, Massachusetts). Comparison of the number of AEs between treatments was made using the Fisher exact test; a P value of <0.05 was considered statistically significant.

Pharmacokinetic and Statistical Analyses

To assess the bioequivalence of monotherapy and combination therapy, AUC within a dosing interval at steady state ($AUC_{\tau,ss}$) and $C_{max,ss}$ were considered the primary variables. Pharmacokinetic parameters ($AUC_{\tau,ss}$, $C_{max,ss}$) were determined using noncompart-

Table I. Baseline demographic and clinical characteristics of the healthy Korean subjects in this study of the tolerability and pharmacokinetic properties of treatment with revaprazan 200 mg and itopride 150 mg administered as monotherapy and in combination.

Characteristic	Treatment Sequence*						All Subjects (n = 30)	P
	ABC (n = 5)	CAB (n = 5)	BCA (n = 5)	CBA (n = 5)	BAC (n = 5)	ACB (n = 5)		
Age, mean (SD), y	35 (5.48)	29.60 (5.94)	31.40 (10.99)	29.60 (6.58)	31.80 (3.77)	34 (10.15)	31.90 (7.22)	0.7311†
Height, mean (SD), cm	172 (4.36)	175.98 (4.51)	173.80 (4.92)	176.66 (4.64)	178.62 (5.75)	168.38 (6.06)	174.24 (5.75)	0.0997†
Weight, mean (SD), kg	68.72 (4.41)	71 (4.96)	71.52 (4.59)	68.16 (8.20)	71.66 (8.20)	62.20 (9.21)	68.88 (7.10)	0.3036†
Habitual substance use, no. (%)								
Alcohol	3 (60)	2 (40)	3 (60)	3 (60)	1 (20)	0	12 (40)	0.2832‡
Caffeine	2 (40)	3 (60)	2 (40)	1 (20)	2 (40)	2 (40)	40 (12)	0.9884‡
Nicotine	0	2 (40)	3 (60)	1 (20)	2 (40)	1 (20)	9 (30)	0.5894‡

*Treatment A: revaprazan 200 mg once daily; treatment B: itopride 50 mg TID; treatment C: revaprazan 200 mg once daily + itopride 50 mg TID. Each treatment was administered for 7 days, with a 7-day washout between periods.
†Kruskal-Wallis test.
‡Fisher's exact test.

mental methods with WinNonlin version 6.1 (Pharsight Corporation, Mountain View, California) on actual sampling times.[39] $C_{max,ss}$ was obtained directly from plasma concentration–time curves. $AUC_{\tau,ss}$ was calculated using linear trapezoidal summation in the increasing period and log/linear trapezoidal summation in the decreasing period.

Log-transformed pharmacokinetic parameters were analyzed using a linear mixed-effects model, with treatment, sequence, period as fixed factors and subjects within sequence as a random factor. The resulting 90% CIs of the ratios of geometric means of combination therapy/monotherapy for these variables were used to determine bioequivalence, defined as a range between 0.80 and 1.25.[40]

RESULTS

Study Population

A total of 30 healthy male subjects aged 20 to 50 years were enrolled into the study. Twenty-seven subjects completed all treatment periods with no protocol violations. Three subjects dropped out of the study by withdrawal of consent due to personal reasons. One subject withdrew after completing the first period, and the other 2 dropped out after the second period. One of these 2 subjects completed the entire course of treatment with revaprazan monotherapy but not itopride monotherapy. Thus, pharmacokinetic data for revaprazan were based on 28 subjects, while data collected from 27 subjects were used for itopride. The tolerability population included all 30 subjects. Disposition of the subjects is shown in **Figure 1**.

This study was well balanced with respect to age, weight, and height; mean (SD) age was 31.90 (7.22) years; mean (SD) weight was 68.88 (7.10) kg; and mean (SD) height was 174.24 (5.75) cm (**Table I**).

Pharmacokinetic and Statistical Analysis

Table II shows the pharmacokinetic properties of revaprazan and itopride. Mean $AUC_{\tau,ss}$ values of revaprazan monotherapy and revaprazan + itopride combination therapy were 2573.95 and 2370.49 ng · h/mL, respectively; corresponding mean $C_{max,ss}$ values were 364.58 and 328.23 ng/mL; and corresponding mean CL_{ss}/F values were 96.07 and 98.31 L/h, respectively. Median $T_{max,ss}$ values of were 2.00 hours for both (**Figure 2**A).

Table III shows the geometric mean ratios (90% CI) for the pharmacokinetic parameters after log-transfor-

Table II. Pharmacokinetic parameters of steady-state revaprazan 200 mg and itopride 150 mg administered as monotherapy and in combination in healthy Korean subjects. Data are mean (range) unless otherwise specified.

	Revaprazan (n = 28)		Itopride (n = 27)	
Parameter[†]	Monotherapy	Combination With Itopride	Monotherapy	Combination With Revaprazan
$AUC_{\tau,ss}$, ng · h/mL	2573.95 (788.17–8403.39)	2370.49 (969.49–6310.49)	565.03 (343.85–1118.76)	640.67 (385.13–1704.59)
$C_{max,ss}$, ng/mL	364.58 (133.82–1002.38)	328.23 (126.09–923.16)	220.81 (112.23–395.87)	243.89 (96.52–634.31)
CL_{ss}/F, L/h	96.07 (23.80–253.75)	98.31 (31.69–206.29)	283.12 (134.08–436.24)	256.81 (88.00–389.48)
$T_{max,ss}$, median (range), h	2.00 (1.50–4.00)	2.00 (1.50–4.00)	0.75 (0.50–3.00)	0.75 (0.48–4.00)

CL_{ss}/F = oral clearance at steady state.

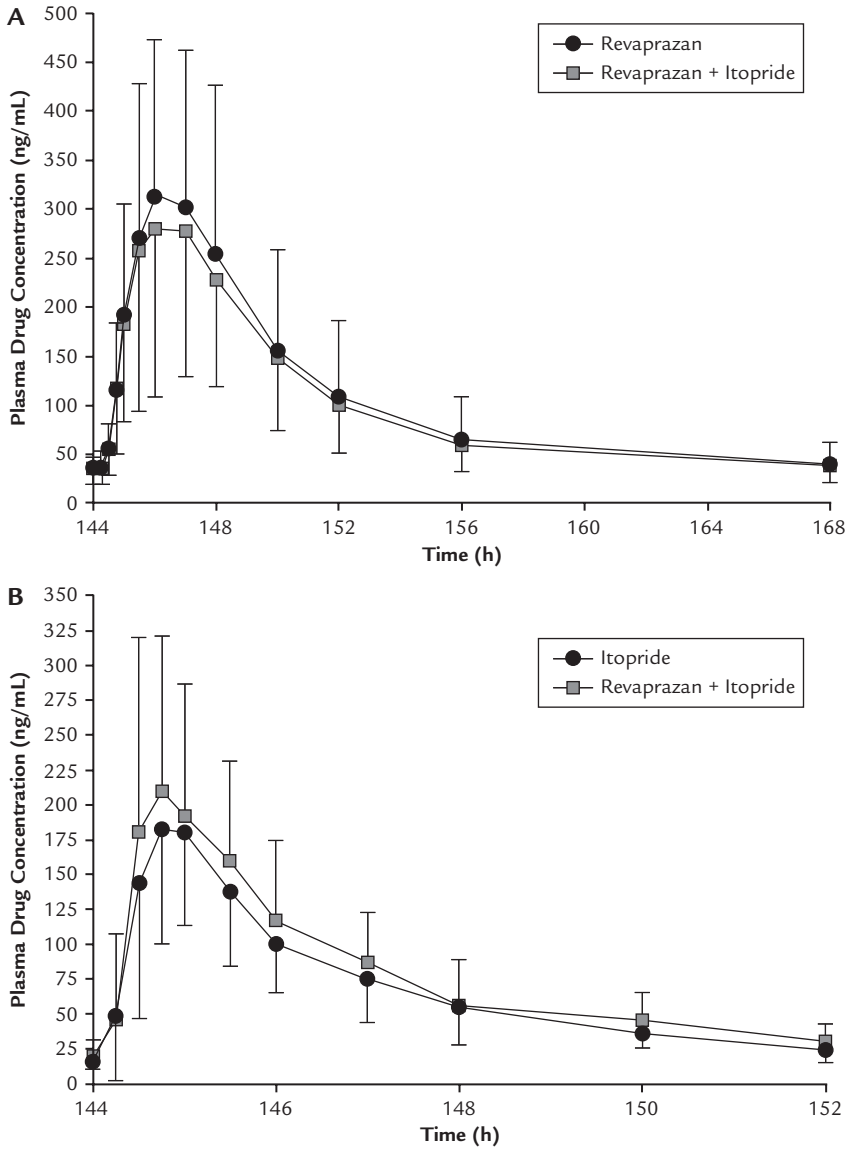

Figure 2. Plasma concentration-time profiles of steady-state (A) revaprazan 200 mg and (B) itopride 150 mg administered as monotherapy and in combination in healthy Korean subjects.

mation of the data. The 90% CI of the $C_{max,ss}$ ratio was 0.84 to 1.00 and the 90% CI of $AUC_{\tau,ss}$ ratio was 0.89 to 1.03. Thus, the primary parameters for evaluating bioequivalence all fell within the range of 0.80 to 1.25.

Mean $AUC_{\tau,ss}$ values of itopride monotherapy and itopride + revaprazan combination therapy were 565.03 and 640.67 ng · h/mL, respectively; corresponding mean $C_{max,ss}$ values were 220.81 and 243.89 ng/mL; and corresponding mean CL_{ss}/F values were 283.12 and 256.81 L/h. Median $T_{max,ss}$ values were 0.75 hours for both (Figure 2B). The 90% CI of $C_{max,ss}$ ratio was 0.96 to 1.20 and the 90% CI of $AUC_{\tau,ss}$ ratio was 1.06 to 1.18. Thus the ratios were all within the bioequivalence interval of 0.80 to 1.25, as with revaprazan (Table III).

Tolerability

The tolerability population included 30 subjects. Fifteen AEs were reported in 8 subjects. Taking into account the time course and onset of AE, the time interval of drug administration, and other possible

Table III. Geometric mean ratios (90% CI) of the pharmacokinetic properties of steady-state revaprazan 200 mg and itopride 150 mg administered as monotherapy (ref) and in combination in healthy Korean subjects.

Parameter	Revaprazan (n = 28)	Itopride (n = 27)
$C_{max,ss}$	0.92 (0.84–1.00)	1.07 (0.96–1.20)
$AUC_{\tau,ss}$	0.96 (0.89–1.03)	1.12 (1.06–1.18)

causes leading to similar symptoms based on medical knowledge, the investigator classified AEs by relationship to study drug. AEs that were certainly, probably, or possibly related to drug uptake were considered as adverse drug reactions (ADRs). Five AEs reported in 4 subjects were determined as possibly being related to the treatment. The symptoms were diarrhea in 2 cases, abdominal discomfort in 1 case, nausea in 1 case, and dizziness in 1 case. The most frequently reported AEs were gastrointestinal disorders (6 events in 4 subjects) (**Table IV**). No clinically significant differences in tolerability were identified between treatment groups (**Table V**). All reported AEs were mild and recovery was complete. No serious AEs or AEs causing premature discontinuation from the study were reported.

DISCUSSION

Dyspepsia is a widely used medical term that usually describes upper abdominal discomfort or pain.[41] It has a prevalence of 20% to 40% in developed countries. Among patients with dyspepsia, 60% have been diagnosed with FD. According to recent studies, FD not only greatly reduces quality of life but also increases health care costs.[1,42] Until now, there has been no satisfactory treatment for FD, and some patients are prescribed >2 drugs in combination to control the symptoms.[43] PPIs and prokinetic agents have been considered effective in the treatment of FD.[3,11,13,23,32–34] However, long-term use of PPIs may cause atopic gastritis and hypergastrinemia.[44-47] Revaprazan, a selective P-CAB, has rapid and effective acid-suppressive activity and an efficacy similar to those of traditional PPIs, without causing hypergastrinemia.[28–30,48] Therefore, combined with prokinetic agents such as itopride, revaprazan is expected to have similar treatment effects for FD, without increasing gastrin levels.[25–27]

Revaprazan is metabolized through hepatic cytochrome P450 (CYP) enzymes, whereas itopride is metabolized through flavinemonooxygenase.[49] Due to their different metabolic pathways, it was predicted that the risk for drug–drug interactions would be low. However, information about drug–drug interactions with revaprazan is still insufficient. A recent study revealed interactions between revaprazan and warfarin, although not by competitively interrupting the CYP isozyme system.[50] In addition to drug–drug interactions via CYP enzymes, several conventional PPIs have been reported to have various interactions with other drugs by reducing the bioavailability of HIV protease inhibitors due to the change in intragastric pH, and then solubility; inhibiting the efflux transporter system; increasing transepithelial paracellular gastric leak; and altering renal elimination of methotrexate.[51–54] Because of these findings, the possibility of an interaction between revaprazan and itopride could not be ruled out.

The present clinical trial was conducted to evaluate the pharmacokinetics and tolerability of revaprazan with or without itopride, as well as to determine any pharmacokinetic interactions between these 2 drugs. Fifteen mild AEs were reported in 8 of the 30 healthy male Korean subjects who took part in the study. All individuals completely recovered and no new or clinically significant tolerability concerns arose. On bioequivalence analysis, the 90% CIs of the log-transformed ratios of the pharmacokinetic parameters $C_{max,ss}$ and $AUC_{\tau,ss}$ for revaprazan and itopride monotherapy and combination therapy fell within the standard bioequivalence range of 0.80 to 1.25. No differences in pharmacokinetic parameters were found with the data normalized for dose by weight.

In a previous study, the pharmacokinetic characteristics of revaprazan were evaluated.[29] Volunteers were randomly allocated to single-dose groups of 60, 100, 150, 200, or 300 mg, or to multiple-dose groups of 150 or 300 mg, add administered once daily for 7 days. The group receiving the 200-mg single dose showed 1343.1 ng · h/mL for $AUC_{0-\infty}$, 361.4 ng/mL for $C_{max,}$ and 2.1 hours for T_{max}. The $AUC_{\tau,ss}$, C_{max}, and T_{max} values for the 7-day multiple-dose group receiving 150 mg of revaprazan were 1391.7 ng · h/mL, 279.3 ng/mL, and 1.4 hours, respectively. When 300 mg of revaprazan was administered, the $AUC_{\tau,ss}$, C_{max}, and T_{max} values were 3281.8 ng · h/mL, 654.1 ng/mL, and 2.2 hours respectively. The C_{max} and T_{max} values were similar to those in the present study. The $AUC_{\tau,ss}$ was also similar to

Table IV. Tolerability of revaprazan 200 mg and itopride 150 mg administered as monotherapy and in combination in healthy Korean subjects.* Data are numbers of AEs.

	Revaprazan Monotherapy (n = 30)		Itopride Monotherapy (n = 28)		Revaprazan + Itopride Combination Treatment (n = 28)		
AE	Treatment Related	Not Treatment Related	Treatment Related	Not Treatment Related	Treatment Related	Not Treatment Related	Totals
Nervous system disorders							
Dizziness	1	0	0	0	0	1	2
Tremor perioral	0	1	0	0	0	0	1
Respiratory, thoracic and mediastinal disorders							
Sore throat	0	1	0	0	0	0	1
Rhinorrhea	0	0	0	1	0	1	2
General disorders and administration-site conditions							
Fatigue	0	1	0	0	0	0	1
Musculoskeletal and connective tissue disorders							
Joint stiffness	0	1	0	0	0	0	1
Gastrointestinal disorders							
Epigastric pain	0	1	0	0	0	0	1
Epigastric soreness	0	1	0	0	0	0	1
Nausea	0	0	1	0	0	0	1
Diarrhea	0	0	0	0	2	0	2
Abdominal discomfort	0	0	0	0	1	0	1
Injury, poisoning and procedural complications							
Forehead skin abrasion	0	0	0	0	0	1	1
Totals	1	6	1	1	3	3	15

*Treatment related = certainly, probably, or possibly related to drug uptake; not treatment related = unlikely or definitely not related to drug uptake.

that in the present study, considering the doses administered, and the dose-proportional characteristics of revaprazan between 150 and 300 mg. In the previous study, the accumulation index (AI) calculated for 150 mg of revaprazan was 1.5, and for 300 mg of revaprazan, was 1.1. By applying these AI values to 200 mg of revaprazan, the $AUC_{\tau,ss}$ would fall in the range of 1477.41 and 2014.65 ng · h/mL. Considering that the previous study of parallel, not crossover, design, and that 1 group was of a relatively small sample size (6 subjects), the results from the present study can be used as an extension of the existing findings on the pharmacokinetic properties of revaprazan.

For itopride, a previous bioequivalence study reported AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and T_{max} ratios for single-dose (50-mg) administration, which were 1041.69 ng · h/mL, 1089.93 ng · h/mL, 284.76 ng/mL, and 0.9 hours, respectively.[55] The C_{max} and T_{max} values were comparable to those in the present study, whereas AUC values in the present study were less. Subjects enrolled in the study were given 50 mg of itopride TID and were expected to take the drug regularly at 9 AM, 1 PM,

Table V. Statistical analysis of the tolerability of combination treatment with revaprazan 200 mg and itopride 150 mg administered as monotherapy and in combination in healthy Korean subjects.*

	Revaprazan Monotherapy (n = 30)		Itopride Monotherapy (n = 28)		Revaprazan + Itopride Combination Treatment (n = 28)		
Event Type	No. of Subjects	No. of Events	No. of Subjects	No. of Events	No. of Subjects	No. of Events	$P^{\dagger}$
AEs	3	7	2	2	4	6	0.76
ADRs	1	1	1	1	2	3	0.84

ADR = adverse drug reaction (defined as an AE certainly, probably, or possibly related to use of the study drug); AE = adverse event.
*All events were considered mild.
†For comparing the incidence of AEs or ADRs between groups, *P* was obtain.

and 6 PM. For calculating $AUC_{\tau,ss}$, because it was not a constant τ value, τ in the present study was set as an average of real dosing time interval—8 hours. Because the time interval between 6 PM and 9 AM was long, it may have led to an underestimation of $AUC_{\tau,ss}$. To accurately compare monotherapy to combination therapy, the administration times were established around typical meal times, with drug uptake 30 minutes before meals. In doing so, effects from food were minimized, subject compliance was obtained, and clinical conditions were more realistically reflected. To minimize large fluctuations in drug-administration times between subjects, they were asked to take the drugs at regular times and to record these times in a journal.

The present study was conducted only in healthy male subjects because of the focus on the interaction between 2 drugs. It was assumed that sex would not affect drug interaction much; although there are differences in the pharmacokinetic properties between combined therapy and monotherapy in men, these differences also apply in women. Excluding women also eliminated the risk for teratogenic effects. The labeling of revaprazan and itopride (KFDA approved in 2005 and 2007, respectively), includes warnings about the risks in the pregnant and breastfeeding women based on findings from animal studies.

This study showed comparable pharmacokinetics of revaprazan and itopride monotherapy and combination therapy in healthy male Korean subjects. Comparable pharmacokinetic features are expected in patients with FB. Based on a literature search, no available studies have compared the effectiveness of monotherapy versus combination therapy of revaprazan and itopride in a large group of patients. In the near future, more studies may be conducted to develop more effective and safer treatment standards.

CONCLUSIONS

The present study in healthy male Korean volunteers, no clinically significant pharmacokinetic differences were found between revaprazan 200 mg and itopride 150 mg, administered as monotherapy and as combination therapy. All treatments were generally well-tolerated.

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CONFLICTS OF INTEREST

This study was sponsored by Yuhan Corporation, Seoul, Korea. Dr. Jang is an employee of Yuhan Corporation.

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