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Research Article

Pharmacokinetic and Pharmacodynamic Evaluation of a Sodium Bicarbonate Combination of Rabeprazole, a Proton-Pump Inhibitor, in Healthy Subjects

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Abstract

Purpose: Proton-pump inhibitors, such as rabeprazole, are prone to degradation in stomach acid. The use of Enteric-Coated (EC) forms minimizes this problem; however, these forms have slower onset time. The Pharmacokinetics (PK) and Pharmacodynamics (PD) of rabeprazole in a Fixed-Dose Combination (FDC) tablet with sodium bicarbonate, which was used to raise the intragastric pH, and in a conventional EC tablet were compared.

Materials and methods: A randomized, open-label, multiple-dose, 2-treatment, 2-sequence, 2-period, crossover study of 40 subjects was conducted to evaluate PK and PD characteristics. Eligible subjects received with 20 mg rabeprazole and 800 mg sodium bicarbonate FDC or 20 mg rabeprazole EC tablets for 7 days during each period. Serial blood samples were collected for up to 24 hours on days 1 and 7. Using non compartmental methods, rabeprazole PK parameters were estimated. Ambulatory pH monitoring was performed on days -1, 1, and 7 to determine PD parameters. Quantitative comparison was conducted based on the 90% Confidence Interval (90% CI) of the area under the concentration vs. time curve over the dosing interval (AUCtau,ss) and the percentage decrease from baseline in Integrated Gastric Acidity (% IGA) after 24 hours with the criteria that the FDC-to-EC tablet ratio fell within the range of 0.80-1.25.

Results: After 7 days of administration, total rabeprazole exposures were similar following treatment with sodium bicarbonate FDC and EC tablets (90% CI of 1.0880-1.1731 for AUCtau,ss). With a 90% CI of 0.8937-1.0448 for the fall in % IGA from baseline, the two formulations had a similar acid suppression effect. All adverse events were mild and transient.

Conclusion: The rabeprazole and sodium bicarbonate FDC formulation led to a shorter time at which the maximum concentration was reached than the rabeprazole EC form without altering the total rabeprazole exposure or the intragastric acid suppression effect after multiple administrations.

Keywords: Clinical trial; Intragastric acid suppression; Phase I; Comparative PK/PD

Abbreviations

AUC_{tau}: Area Under the Curve During a Dosage Interval (Tau) After a Single Dose; $AUC_{tau,ss}$: Area Under the Curve During Tau after Multiple Doses; C_{max}: Maximum Plasma Concentration after a Single Dose; $C_{max,ss}$: Maximum Plasma Concentration During Tau after Multiple Doses; EDTA: Ethylenediaminetetraacetic Acid; IGA: Integrated Gastric Acidity; MS/MS: Tandem Mass Spectrometry; MRM: Multiple Reaction Monitoring; PD: Pharmacodynamic; PK: Pharmacokinetic; $t_{1/2}$: Terminal Half-Life After a Single Dose; $t_{1/2,ss}$: Terminal Half-Life After Multiple Doses; T_{max}: Time to Reach Maximum Plasma Concentration after a Single Dose; $T_{max,ss}$: Time to Reach Maximum Plasma Concentration Following Drug Administration after Multiple Doses

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Introduction

Proton-Pump Inhibitors (PPIs) are a class of drugs that are widely used for the treatment and prevention of early symptoms caused by gastric acid in the stomach, duodenum, and esophagus, and they function through the suppression of gastric acid secretion [1]. Commonly used orally administered PPI formulations are delivered to the parietal cells in the form of a prodrug, and the drug substance passes the stomach and is absorbed into the systemic circulation from the upper duodenum and the small intestine [2,3]. The delivered prodrug is then converted into an active form, which irreversibly binds to the proton-pump located within the parietal cells, resulting in inhibition of H^+ secretion into the gastric lumen [3].

First-generation PPIs, such as omeprazole and pantoprazole, are mainly metabolized by the Cytochrome p450 (CYP) 2C19 enzyme, resulting in drug-drug interactions across different enzyme substrates or differences in pharmacokinetic characteristics due to genetic polymorphisms, which remain unaddressed [2,3]. However, second-generation PPIs with lowered dependency on CYP2C19, including

esomeprazole and rabeprazole, have been developed, and these drugs not only compensate for the shortcomings of the first-generation PPIs but also elicit equal or superior inhibitory effects [4-8]. In addition, rabeprazole shows nonenzymatic metabolic properties in which glutathione reductive cleavage is involved, which overcomes the long-term adverse effects caused by the irreversibility of other PPIs [9]. Because PPIs are weak bases with low stability in the acidic conditions of the stomach, Enteric-Coated (EC) forms have been developed to induce absorption in the intestine while minimizing their degradation due to acid in the stomach [10-12]. However, these formulations exhibit a slower absorption time than the immediate-release formulations, resulting in a slower onset time. In the clinic, the use of PPIs has been coupled with rescue antacids or combination therapy with H_2 blockers to overcome these onset time-related issues [13,14].

Fixed-Dose Combination (FDC) formulations of two or more drug substances are widely being developed and used to improve medication compliance during combination treatment [15-18]. The FDC formulation can be used not only in combination treatment but also in augmentation treatment, which involves the addition of a medication that is not considered a standard treatment to a typically used medication and is expected to exert better clinical outcome (e.g., the use of thyroid supplementation with an antidepressant agent for depression) [19]. With the aim of preserving the advantages of EC formulations, which exhibit faster absorption, PPI and sodium bicarbonate FDCs are being developed to prevent acid degradation of the PPI substance by elevating the intragastric pH and allowing absorption from the proximal duodenum [20,21].

In this study, the pharmacokinetic and pharmacodynamic characteristics of rabeprazole and sodium bicarbonate FDC tablets and those of the EC tablet formulation of rabeprazole in healthy volunteers were compared.

Materials and Methods

The investigated drug, ethics approval, and consent to participate

To compare the pharmacokinetic and pharmacodynamic characteristics of 20 mg rabeprazole used as a single constituent with those of the fixed-dose combination with 800 mg sodium bicarbonate, multiple doses of each formulation were administered for 7 days in subjects who were eligible for study participation per the inclusion and exclusion criteria of the study. All subjects provided informed consent before participation in any procedure.

The study protocol, including the informed consent form, was approved by the Chungbuk National University Hospital Institutional Review Board, and the study was conducted at the Clinical Trials Center, Chungbuk National University Hospital, Cheongju, Korea (Clinical Trials.gov registry no: NCT05282914, registered on 16.03.2022). The study was conducted under the principles stipulated in the International Council on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki as amended in October 2013 (Fortaleza, Brazil) [22,23].

Study design

Volunteers between the ages of 19 and 55 years with a Body Mass Index (BMI) of 18.0 kg/m^2 to 30.0 kg/m^2, who were considered as healthy, and were subjected to clinical assessments (i.e., physical examination, clinical laboratory tests, etc.) performed at the time of screening were considered for participation. The grouping of eligible subjects was randomized in an open-label, multiple-dose, 2-treatment, 2-period, 2-sequence crossover study design. Twenty subjects were allocated to each sequence, with at least 2 weeks of washout between the periods. An FDC tablet of 20 mg rabeprazole and 800 mg of sodium bicarbonate or a 20 mg rabeprazole EC tablet was orally administered with 150 mL of water as once-daily doses for 7 days under fasting conditions. All subjects remained within the clinical trial center for each treatment period (Day -2 to Day 8) including the day during which baseline measurements were performed.

For pharmacodynamic assessment, ambulatory 24-hour pH monitoring was implemented at baseline (Day -1) and at the single-dose (Day 1) and multiple-dose (Day 7) time points. The pH recording started at least 30 minutes prior to the time scheduled for drug administration and continued for 24 hours. During the pH recording, the subjects were asked to remain in an upright position (seated or standing up), and measurements were performed during the daytime. The subjects were prevented from consuming any food for at least 10 hours prior to dosing to maintain an empty stomach. For pharmacokinetic assessment, blood samples were collected in tubes spray-dried with Ethylenediaminetetraacetic Acid (EDTA) before drug administration and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 hours post administration on Days 1 and 7 in each period, Day 2 before drug administration, and Day 7, 24 hours post administration (Day 8). To separate plasma from blood samples, the samples were centrifuged at 2000 × g for 10 minutes at 4°C. The supernatant was then aliquoted to be stored below -70°C until the time of concentration analysis.

Vigorous exercise, blood donation/transfusion, excessive smoking, and the consumption of alcohol and caffeinated drinks were prohibited, with no concomitant medications or food containing grapefruit allowed throughout the entire study period. The subjects were required to use clinically acceptable contraceptives until the end of the study.

Determination of plasma rabeprazole concentration

The rabeprazole concentration assay was performed using a validated method with an Agilent 1200 series RRLC liquid chromatography system (Agilent, CA, USA) with an Aegispak C18-L column (5 µm, 2.0 mm × 50 mm, Young Jin Biochrom Co., Ltd., Gyeonggi-do, Korea) and a 6410B Triple Quadrupole MS/MS (tandem mass spectrometry) system (Agilent, CA, USA). For quantification of rabeprazole levels, the multiple action monitoring (MRM) modes was implemented using the positive ion electrospray method. For assessments of rabeprazole and rabeprazole-d4 (internal standard) levels, MRM transitions of m/z=360.1 → 242.0 and 364.1 → 242.0 were monitored, respectively.

Stock solutions of rabeprazole and rabeprazole-d4 (1000 µg/mL) were diluted in 50% methanol (0.1% triethylamine) to prepare the working solutions. In cases of out-of-range values, the plasma samples were diluted with blank human plasma to bring the concentration within the calibration range. The calibration standards were prepared by spiking blank plasma samples with rabeprazole concentrations ranging from 5.00 ng/mL to 2000 ng/mL. The correlation coefficient (r^2) value of 0.9991 indicated that the calibration curve was linear within these ranges. The quality control samples were prepared for each analysis batch used for rabeprazole measurements, and the accuracy range expressed as the percentage of the deviation of the mean from the theoretical concentration and relative standard deviations for the

precision range were -0.3%-2.9% and 1.8-2.4%, respectively.

Ambulatory pH monitoring

By using an ambulatory pH recording device (Digitrapper™ Recorder, MN, USA), intragastric pH monitoring was performed for 24 hours or more. The recording device and the catheters were calibrated using standard buffer solutions (pH 4, pH 7, and distilled water) prior to the insertion of each catheter. For pH monitoring, a calibrated pH catheter was inserted into the stomach *via* one of the nostrils until the gastric pH detected by the distal sensor fell to a level of approximately pH 2.5. The length of the catheter placed during the first insertion (continuous monitoring for baseline and Day 1) was recorded in centimeters and used during the insertion of the following catheter (Day 7). Before the administration of the study drugs, the esophageal pH (proximal sensor) and gastric pH (distal sensor) were maintained at approximately pH 6-7 and 2.5, respectively. The subjects were maintained in an upright position during the pH monitoring period, which was performed during the daytime.

Pharmacokinetic evaluation

Plasma concentrations of rabeprazole over time were analyzed to evaluate the Pharmacokinetic (PK) parameters. The parameters used in PK evaluation were the peak concentration after single (C_{max}) and multiple doses ($C_{max,ss}$), the time to peak concentration after single (T_{max}) and multiple doses ($T_{max,ss}$), the area under the concentration-time curve during the dosing interval after single (AUC_{tau}) and multiple doses ($AUC_{tau,ss}$), and the terminal half-life after single ($t_{1/2}$) and multiple doses ($t_{1/2,ss}$). The AUC_{tau} was calculated using the linear up/log down method. Observed concentrations and actual times were used to determine the peak concentration (C_{max} and $C_{max,ss}$) and time to peak concentration (T_{max} and $T_{max,ss}$) of rabeprazole. The terminal half-life ($t_{1/2}$ and $t_{1/2,ss}$) was calculated as $\ln(2)/\lambda_z$ (λ_z: elimination rate constant calculated by linear regression of the terminal slope of the plasma concentration *vs.* time curve).

By using Phoenix® WinNonlin® (version 6.4, Certara USA Inc., NJ, USA), the PK parameters were estimated for comparison between the two formulations. For comparison between the rabeprazole and sodium bicarbonate FDC tablet and rabeprazole EC tablet, a mixed effect model was applied to the exponentiated geometric mean differences and the corresponding 90% Confidence Intervals (CIs) of the C_{max}, AUC_{tau}, $C_{max,ss}$ and $AUC_{tau,ss}$. It was concluded that there was no difference in the extent of exposure between individuals who received the two different formulations if the 90% CIs of these parameters fell within the range of 0.80-1.25 [24]. All statistical analyses were performed using SAS® analytics Pro (version 9.4, SAS Institute Inc., Cary, NC, USA).

Pharmacodynamic evaluation

As the primary Pharmacodynamic (PD) parameter, the percent decrease in the Integrated Gastric Acidity (IGA) from baseline over 24 hours after multiple administrations of rabeprazole and sodium bicarbonate FDC tablets or rabeprazole EC tablets for 7 days was evaluated. Furthermore, the percent decrease in the IGA from baseline over 24 hours after a single dose, percentage of time in which gastric pH was >4 over 24 hours, and median intragastric pH were evaluated. For the calculation of IGA, the previously reported 'weighted intragastric acidity' calculation method was implemented as follows [25].

1. Acid concentration (mM)= 1000 × 10-pH.
2. Acidity (mmol•h/L) = (acid in mM at time't' + acid in mM at time 't-1')/2 × ('t'-'t -1').
3. Values for acidity were summed cumulatively every second.
4. Integrated acidity was expressed as 'mM × time', i.e., mmol•h/L.
5. Values for integrated acidity were analyzed for each hour of the 24-h recording period.

The percentage decrease from baseline was calculated by subtracting the IGA after dosing from the baseline value, dividing by the baseline IGA, and multiplying by one hundred. For comparison between the rabeprazole and sodium bicarbonate FDC tablet and the rabeprazole EC tablet, an identical method as that used during PK evaluation was used to assess the percent decrease in the IGA from baseline over 24 hours. It was concluded that there was no difference in intragastric acid suppression between the two formulations if the 90% CIs of these parameters fell within the range of 0.80-1.25 [24]. All statistical analyses were performed using SAS® analytics Pro (version 9.4, SAS Institute Inc., Cary, NC, USA).

Tolerability assessment

Vital sign assessments (systolic and diastolic blood pressures and pulse rate), physical examinations, and assessments of adverse events were conducted as tolerability assessments from the time of the administration of the study drug until the end of the study. Data regarding the adverse events reported by the subjects were collected using nonleading open questions and individual interviews. The use of concomitant medications was allowed for the treatment of adverse events under the investigator's supervision.

Results

Subjects

Forty-one subjects were randomized and included in the full analysis set, and their demographic characteristics were evaluated. Three subjects withdrew consent before drug administration; the remaining 38 subjects who received the investigational drug at least once were included for tolerability assessment. Among these subjects, a total of 35 completed the study and were included in the PK and PD evaluations.

The mean ± standard deviations values for age, height, weight, and BMI of the 41 subjects enrolled were 29.8 ± 8.5 years, 173.3 ± 4.6 cm, 71.9 ± 9.1 kg, and 23.9 ± 2.7 kg/m^2, respectively. There were no significant differences across the sequence groups in terms of demographic characteristics, including age, height, weight, and BMI, with P values of 0.5924, 0.6290, 0.8320, and 0.5879, respectively.

Rabeprazole pharmacokinetics

The mean plasma rabeprazole concentration-time curves after a single and multiple oral administrations of the 20 mg rabeprazole FDC tablet with 800 mg sodium bicarbonate and the 20 mg rabeprazole EC tablet in healthy subjects are shown in Figure 1. The rabeprazole FDC tablet with sodium bicarbonate exhibited a shorter time to peak maximum concentration (T_{max} and $T_{max,ss}$) than the rabeprazole EC tablet after both single and multiple administrations. The elimination half-life after single and multiple doses of both formulations was approximately 1.7 hours (Figure 1 and Table 1).

Regarding the differences resulting from the administration of the formulations, the maximum concentration of rabeprazole achieved using the sodium bicarbonate FDC tablet was 1.4- and 1.6-fold greater

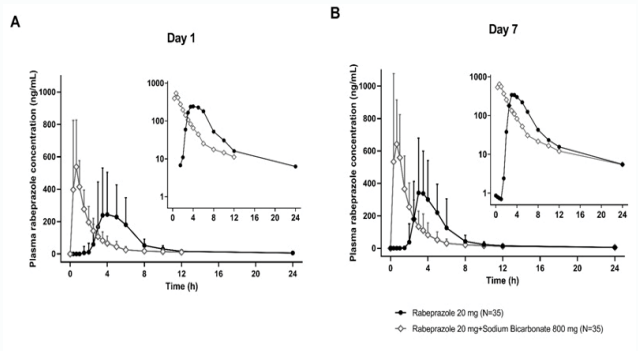

Figure 1: Mean plasma concentration versus time curves after multiple oral doses of 20 mg rabeprazole and 800 mg sodium bicarbonate (-◇-) as Fixed-Dose Combination (FDC) tablets and 20 mg rabeprazole (-●-) as Enteric-Coated (EC) tablets and in healthy subjects (N=25); A on Day 1, and B on Day 7. The inset shows the semilog scale plots.

than that achieved using the EC tablet after a single and multiple doses, respectively. (Table 1 and Figure 2A) However, the overall extent of rabeprazole exposure was similar in those who received each formulation considering the result that the point estimates and the 90% CI of the natural log-transformed rabeprazole $AUC_{tau,ss}$ between the two formulations fell within 0.80 and 1.25 (Table 1 and Figure 2B).

Rabeprazole pharmacodynamics

After administration of the rabeprazole FDC tablet with sodium bicarbonate and the rabeprazole EC tablets, the first time at which a pH greater than 4 (pH >4) was reached occurred at 61 and 309 minutes, respectively, on Day 1. On Day 7, the first time points at which the pH was >4 were 34 and 190 minutes for the FDC and EC tablets, respectively (Figure 3). The intragastric PD parameters were similar for the two formulations after 7 days of multiple administrations (Table 2 and Figure 4). The median intragastric pH achieved by both formulations ranged between 1.13 and 1.23 after a single dose, which then rose to 2.53 - 2.56 after multiple doses. The mean ± standard deviation of the percentage of times at which the pH exceeded 4 over 24 hours in the rabeprazole and sodium bicarbonate FDC groups on Day 1 and Day 7 were 26.75 ± 16.15% and 46.90 ± 12.73%, respectively. The value in the rabeprazole EC group on Day 1 was 31.78 ± 12.87% and was 47.69 ± 13.87% on Day 7 (Table 2).

As summarized in Table 2, the percent decrease in the IGA from baseline after single and multiple doses was similar to the point estimates of the geometric mean ratios and the 90% CI values, which fell entirely within the range of 0.80 and 1.25.

Tolerability

There were no serious or moderate to severe adverse events reported in the 38 subjects who received the drug at least once during the study. Twenty-four adverse events observed in 13 subjects were considered to be related to drug administration and included dyspepsia, nausea, constipation, epistaxis, pyrexia, myalgia, tachycardia, hyperhidrosis, abdominal pain, and skin exfoliation (Table 3).

All adverse events were transient and mild in severity, with no clinically significant findings in other tolerability parameters, such as the laboratory test results, vital signs, and physical examination after multiple administrations of rabeprazole with and without the sodium bicarbonate combination in healthy subjects. No concomitant medication for the treatment of Adverse Events (AEs) was required in this study (Table 3).

Discussion

To investigate the pharmacokinetics and pharmacodynamics of rabeprazole FDC tablets with sodium bicarbonate, the corresponding characteristics after multiple doses were compared with those of the conventional rabeprazole formulation in this study. Two weeks of washout between each period was sufficient to allow rabeprazole to be eliminated to the lowest level of quantification as assessed during blood sampling before administration and in the following period in all subjects, and only 3 out of 35 subjects had quantifiable plasma rabeprazole concentrations until the last blood sampling time on day 7 (individual data not shown).

After 7 days of multiple administrations, the two formulations resulted in similar exposure ($AUC_{tau,ss}$) and IGA over 24 hours; thus, similar acid inhibitory effects can be expected (Table 1 and Figure 4). Moreover, the time taken to reach the desired mean intragastric pH after the administration of the rabeprazole FDC tablet with sodium bicarbonate was shorter than that after the administration of the rabeprazole EC tablet (Figure 3). Before the peak rabeprazole exposure and saturation of the fall of acidity were achieved, the percentage of time at which the pH was >4 was lower in those who received the FDC than in those who received the EC (Table 2). Nonetheless, the acidity fluctuation in the EC group was clinically no different from those following multiple administrations of the FDC tablets (Figure 3 and 4). Considering the 4-week or more regimen used to administer the FDC tablet for individuals with acid-related diseases (i.e., GERD (gastroesophageal reflux disease), duodenal ulcers), an equivalent treatment effect in the clinical setting and immediate symptom relief for individuals with GERD are anticipated (Table S1 of Supplementary Material).

Table 1: Pharmacokinetic parameters of rabeprazole after a single and multiple oral administrations in healthy subjects.

Pharmacokinetic Parameter	Rabeprazole 20 mg (N=35)	Rabeprazole 20 mg/Sodium bicarbonate 800 mg (N=35)	Geometric mean ratio (90% confidence interval)
Day 7			
$AUC_{tau,ss}$ (h·ng/mL)	1230.30 (556.70)	1342.12 (623.75)	1.130 (1.088, 1.173)
$C_{max,ss}$ (ng/mL)	616.91 (241.05)	939.55 (336.73)	1.566 (1.392, 1.762)
$T_{max,ss}$ (h)	3.00 [2.00–8.00]	0.67 [0.33-3.50]	-
$t_{1/2,ss}$ (h)	1.68 (1.07)*	1.61 (1.06)	-
Day 1			
AUC_{tau} (h·ng/mL)	1127.68 (509.41)	1060.28 (496.73)	0.973 (0.885, 1.070)
C_{max} (ng/mL)	528.51 (235.46)	714.45 (297.16)	1.386 (1.147, 1.676)
T_{max} (h)	4.00 [2.00–8.02]	0.67 [0.33-1.50]	-
$t_{1/2}$ (h)	1.71 (1.24)*	1.72 (0.82)	-

Data are provided as the mean (standard deviation) except for T_{max} and $T_{max,ss}$, which is expressed as the median [minimum - maximum]

*Only 29 subjects were included due to inability to fit terminal slopes (λz).

Table 2: Change from baseline pharmacodynamic parameters after a single and multiple oral administrations of rabeprazole in healthy subjects.

Parameter	Rabeprazole 20 mg (N=35)	Rabeprazole 20 mg/Sodium bicarbonate 800 mg (N=35)	Geometric mean ratio (90% confidence interval)
Day 7			
24-hour IGA % decrease	74.85 (16.31)	72.82 (15.79)	0.966 (0.894, 1.045)
Mean % time 24-hour intragastric pH > 4	47.69 (13.87)	46.90 (12.73)	-
Median intragastric pH	2.53 (0.99)	2.56 (0.98)	-
Day 1			
24-hour IGA % decrease	59.43 (14.16)	58.25 (19.67)	0.935 (0.827, 1.058)
Mean % time 24-hour intragastric pH > 4	31.78 (12.87)	26.75 (16.15)	-
Median intragastric pH	1.23 (0.95)	1.13 (0.92)	-

Data are provided as the mean (standard deviation) unless otherwise indicated.

Table 3: Drug-related adverse events.

Adverse event		Rabeprazole 20 mg (N=37)	Rabeprazole 20 mg/Sodium bicarbonate 800 mg (N=36)
System of class	**Preferred term**		
Cardiac disorders	Tachycardia	-	1 (1 [2.8])
Gastrointestinal system disorders	Abdominal pain	-	1 (1 [2.8])
	Constipation	1 (1 [2.7])	-
	Dyspepsia	4 (4 [10.8])	5 (5 [13.9])
	Nausea	2 (2 [5.4])	2 (2 [5.6])
General disorders and administration site conditions	Pyrexia	-	1 (1 [2.8])
Musculoskeletal and connective tissue disorders	Myalgia	-	1 (1 [2.8])
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (1 [2.7])	3 (1 [2.8])
Skin and subcutaneous tissue disorders	Hyperhidrosis	1 (1 [2.7])	-
	Skin exfoliation	1 (1 [2.7])	-
Total		10 (10 [27.0])	14 (9 [25.0])

Values are provided as the number of events (number of subjects [% of subjects]).

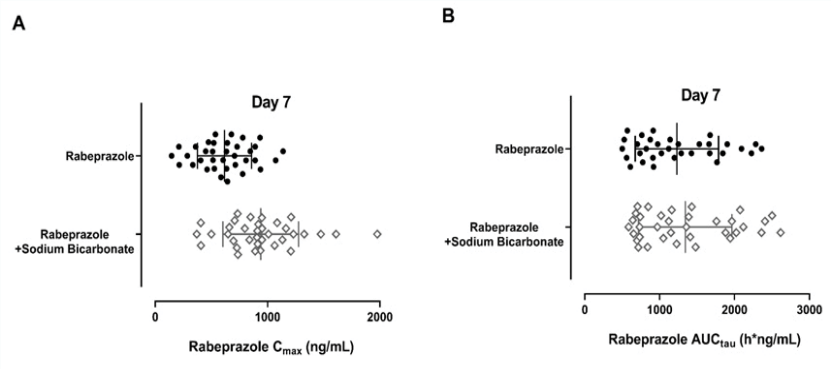

Figure 2: Pharmacokinetic parameters $C_{max,ss}$ (A) and AUC_{tau} (B) after multiple oral doses of rabeprazole and sodium bicarbonate FDC and EC tablets for 7 days in healthy subjects. The three vertical lines represent the median (middle), the first quartile (left), and the third quartile (right).

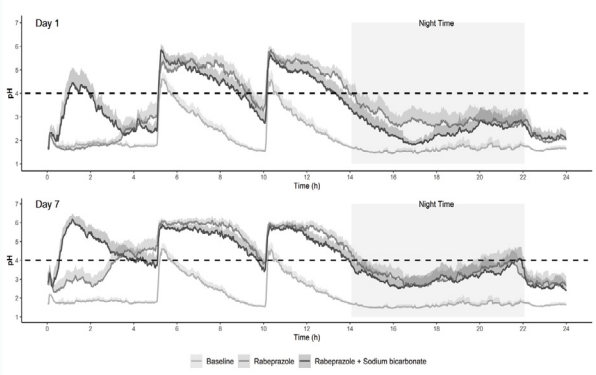

Figure 3: Mean intragastric pH + standard deviation at baseline (light gray), Day 1 (upper), and Day 7 (lower) after administration of rabeprazole and sodium bicarbonate FDC (gray) and rabeprazole EC (dark gray). The shaded area represents the nighttime period.

The use of combination treatment may be required due to multiple indications or to improve the efficacy of monotherapy. Examples of FDC formulations developed as combination treatment for multiple indications and the improvement of monotherapy efficacy include amlodipine with atorvastatin and telmisartan with amlodipine [26,27]. For the treatment of acid reflux diseases, similar approaches have been applied using first- and second-generation PPIs [20,28]. One of the major advantages of these FDCs over EC tablets is that they prevent an unnecessary increase in dosage or a switch to alternate classes of PPI due to lack of an immediate response during the early phase of treatment [29]. The rapid initial elevation in pH is consistent with the forward-shifted Tmax of the sodium bicarbonate FDC tablet; hence the FDC tablet contributed to this rapid inhibition of acid due to its rapid absorption, not just the neutralization effect of the combined antacid (sodium bicarbonate). The similar PK and PD results observed between the conventional EC tablet and the FDC tablet observed in this study indicate that the rabeprazole and sodium

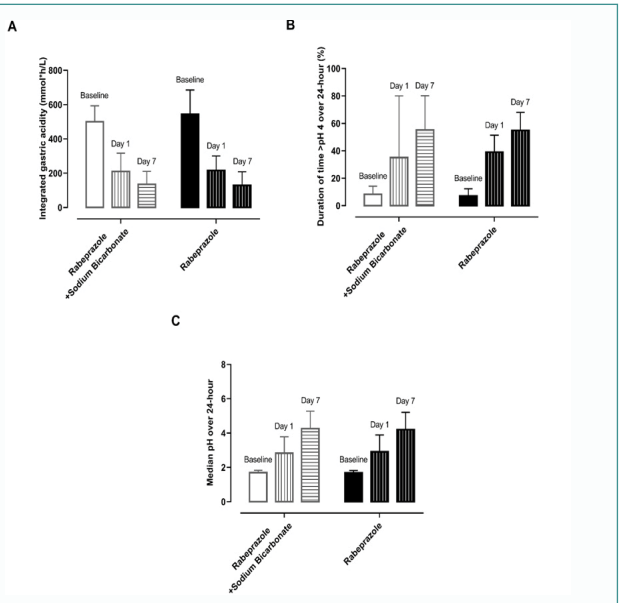

Figure 4: Mean integrated gastric acidity (A), duration of time >pH 4 (B) and median pH (C) over 24 hours at baseline (field), Day 1 (vertical fill), and Day 7 (horizontal lines): rabeprazole and sodium bicarbonate FDC in gray boxes and EC in black boxes. The error bars indicate the standard deviation.

bicarbonate FDC tablet not only exhibits its own strengths, including its potential for minimal interactions with other drugs unlike other PPIs, but it also adequately exhibits the pros of FDCs that have already been marketed.

By assessing measurable PK and PD characteristics in healthy volunteers, the evaluation of the applicability of modified formulations and combination tablets was performed cost-effectively. However, the symptom relief effect cannot be extrapolated from healthy subjects who have different pathophysiologies than GERD patients; for example, the position and sizes of the GERD-causing acid pockets and the possible existence of hiatal hernia were not assessed [30-32]. Although the findings were derived from healthy subjects instead of the indicated group of patients with symptoms of acid reflux, a 20 mg rabeprazole daily dose is known to be adequate to achieve a mean change in pH over 24 hours in GERD patients; hence, similar acid inhibitory effects between the new FDC and EC tablets are expected to occur in patients. Additional confirmation of the clinical outcome will be required in patients with GERD in further studies.

Conclusion

The addition of sodium bicarbonate to rabeprazole sodium shortened the time at which the maximum concentration was reached without altering the total rabeprazole exposure or the intragastric acid suppression effect after multiple administrations.

Ethics approval and informed consent

Prior to the study, the clinical study protocol was approved by the Chungbuk National University Hospital Institutional Review Board. The study was conducted in subjects who provided written informed consent under the principles stipulated in the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice Guideline [22,23].

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Supplementary material

Table S1: Changes in pharmacodynamic parameters from baseline in the first 4 hours after a single and multiple oral administrations of rabeprazole in healthy subjects.

Parameter	Rabeprazole 20 mg (N=35)	Rabeprazole 20 mg/Sodium bicarbonate 800 mg (N=35)	Geometric mean ratio(90% confidence interval)
Day 7			
First 4-hour IGA % decrease	61.06 (22.66)	87.86 (13.22)	1.5876 (1.3450, 1.8739)
Mean % time 4-hour intragastric pH > 4	28.27 (26.77)	62.92 (23.40)	-
Day 1			
First 4-hour IGA % decrease	-9.84 (33.32)	48.13 (46.80)	3.9338 (2.9982, 5.1614)
Mean % time 4-hour intragastric pH > 4	1.68 (6.15)	26.00 (19.04)	-

Data are provided as the mean (standard deviation) unless otherwise indicated.