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Acid Inhibitory Effect of a Combination of Omeprazole and Sodium Bicarbonate (CDFR0209) Compared With Delayed-Release Omeprazole 40 mg Alone in Healthy Adult Male Subjects

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Abstract

CDFR0209, a combination of an immediate-release formulation of omeprazole 40 mg and sodium bicarbonate 1100 mg, has been developed to treat acid-related disorders. We compared the acid inhibitory effects of CDFR0209 and delayed-release omeprazole (omeprazole-DR, Losec 40 mg) after repeated dosing in *Helicobacter pylori*–negative healthy adult male subjects. In this 2-period crossover study, 30 subjects were randomized to CDFR0209 or omeprazole-DR daily for 7 days. An ambulatory continuous 24-hour intragastric pH recording was performed at baseline and on days 1 and 7 of each administration period. Integrated gastric acidity was calculated from time-weighted average hydrogen ion concentrations at each hour of the 24-hour record. An analysis of variance model was used to test the pharmacodynamic equivalence of CDFR0209 and omeprazole-DR, using the natural logarithmic transformation of the percent decrease from baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation. The geometric least-squares mean ratios (CDFR0209/omeprazole-DR) of the percent decrease from baseline in integrated gastric acidity was 0.98 (90%CI, 0.93–1.07). Both CDFR0209 and omeprazole-DR are equally effective in decreasing integrated gastric acidity at steady state.

Keywords

equivalence, 24-hour pH monitoring, immediate-release omeprazole, integrated gastric acidity, pharmacodynamics

Proton pump inhibitors (PPIs) have been very efficacious for the treatment of a variety of acid-related disorders. However, all PPI compounds are weak bases that are acid labile and are rapidly degraded, usually within minutes, in an acidic environment. This pharmacological property requires the active ingredient in all delayed-release oral PPI formulations to have an enteric coating. The coating protects the active ingredient from degradation by gastric acid, but it also delays absorption and subsequent suppression of gastric acid secretion.[1,2]

In 2004, the U.S. Food and Drug Administration approved an immediate-release formulation of omeprazole (Zegerid), and this compound was developed by combining omeprazole with antacid buffer (sodium bicarbonate), which neutralizes gastric acid and protects omeprazole from gastric acid degradation.[3] This product and generics are commercially available in the Unites States and some countries, but has not been

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launched in Korea. Recently, a new combination of an immediate-release formulation of omeprazole 40 mg and sodium bicarbonate 1100 mg (CDFR0209) has been developed in Korea to treat acid-related disorders. The pharmacokinetic profile of CDFR0209 differs significantly from that of a delayed-release omeprazole (omeprazole-DR, Losec 40 mg). In particular, the maximum plasma concentration (C_{max}) of CDFR0209 was 1.2-fold higher than that of omeprazole-DR and was achieved around 30 minutes after a single oral dose on an empty stomach. Other pharmacokinetic parameters, such as area under the concentration–time curve (AUC) and elimination half-life ($t_{1/2}$) were similar to omeprazole-DR (unpublished data).

In this study, we compared the acid inhibitory effects of CDFR0209 and omeprazole-DR, after repeated dosing in *Helicobacter pylori*–negative healthy adult male subjects.

Methods

Subjects

Male volunteers aged 20–45 years and within 20% of ideal body weight were eligible to participate. All subjects were determined to be healthy by a physical examination, medical history, and routine laboratory tests of hematology, blood chemistry, urinalysis, and 12-lead electrocardiogram (ECG) performed within 4 weeks of the first administration of the study drug. Only subjects who were *Helicobacter pylori*–negative based on both ^{13}C urea breath test (UBT) and serology test (*Helicobacter pylori* immunoglobulin G [IgG]) were eligible. Subjects with a history of clinically significant diseases or disorders including renal or hepatic impairment, those with known hypersensitivity to any PPIs, and those with a history of drug abuse were excluded from the study. Antisecretory drugs including PPIs, H_2 receptor antagonists, prokinetic drugs, or any other agents that could affect the pharmacodynamics or absorption of the study drug were prohibited from 2 weeks before randomization and during the entire treatment period.

Study Design

This was a single-center, randomized, open-label, multiple-dose, 2-period, 2-sequence, 2-treatment crossover study. This study was conducted at the Clinical Trial Center of Ajou University Medical Center, Suwon, Republic of Korea. The immediate-release formulation of omeprazole was not available in Korea; the same dosage of omeprazole-DR (Losec 40 mg; Yuhan Corporation, Seoul, Republic of Korea) was chosen as a comparator. The subjects received either CDFR0209 or omeprazole-DR once daily for 7 consecutive days according to a randomization table. The crossover administration of the study drug followed after a washout period of 14 days. On days 1 and 7 of each period, the study drug was administered at approximately 8 AM after an overnight fast of at least 10 hours and followed by a 4-hour postdose fast. A standardized meal was provided to the subjects 4 and 10 hours after the administration of the study drug. Subjects were instructed to lie down only during nighttime hours, between 10 PM and 6 AM, and to avoid smoking and alcohol consumption during the entire treatment period. On day 2, the subjects were discharged after administration of the study drug. On days 3–6, subjects visited the Clinical Trial Center and received the dose once daily at the same time as on day 1.

This study protocol was approved by the Ethics Review Board of Ajou University Medical Center (Suwon, Republic of Korea; IRB no. AJIRB-MED-CT1-14-085) in accordance with the ethical standards for human studies established by the Declaration of Helsinki and its amendments, and the applicable Good Clinical Practice guidelines. All subjects were given detailed written and oral information about the study and were asked to provide written informed consent before being screened for eligibility.

Safety

Adverse events were spontaneously reported by the subjects or solicited by nonleading questioning by the investigators. Physical examination and clinical laboratory tests were performed at baseline, on day 8 of each administration period, and 2 weeks after the administration of the final study drug dose.

Pharmacodynamic and Statistical Analysis

An ambulatory continuous 24-hour intragastric pH recording was performed at baseline (day -1) and on days 1 and 7 of each administration period. Following the overnight fasting, a pH probe was inserted intranasally into the stomach, fixed approximately 5 cm below the lower esophageal sphincter, and connected to a ZepHr recorder (Sandhill Scientific, Inc., Highlands Ranch, Colorado) to digitize and store the pH data. The probes were calibrated with standard buffers (pH 4 and 7) prior to each recording, according to the manufacturer's instructions. Intragastric pH recordings began at 8 AM, with intragastric pH values recorded every 5 seconds for 24 hours. Only subjects who had valid pharmacodynamics parameters estimated for both periods were included in the pharmacodynamic analyses.

Integrated gastric acidity was calculated as previously described, with only slight modifications.[4,5] The brief calculation method was as follows:

(1) Acid concentration (mmol/L) $= 1000 \times 10^{-pH}$.

(2) Acidity (mmol·h/L) = (acid in mmol/L at time t + acid in mmol/L at time t_{-1})/2 × (t − t_{-1}).
(3) Acidity values were summed cumulatively per 5 seconds. Integrated acidity is expressed as mmol/L × time, that is, mmol·h/L.
(4) Integrated acidity was analyzed every hour of the recording.

The primary pharmacodynamics end point was the percent decrease from the baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation. Baseline values for integrated acidity were compared between the 2 treatment periods using the analysis of variance (ANOVA) model. If there were no statistically significant differences in the baseline values for integrated gastric acidity, the baseline values for the 2 periods were averaged when calculating the change from the baseline. Otherwise, the corresponding baseline value for that period was used. The percent decrease from the baseline in integrated gastric acidity on days 1 and 7 was calculated for each subject as 100 × (baseline - day 7 [or day 1])/baseline. An ANOVA model was used to test the pharmacodynamic equivalence of CDFR0209 and omeprazole-DR, using the natural logarithmic transformation of the percent decrease from the baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation, as with the standard bioequivalence methodology for pharmacokinetic parameters. Treatment, sequence, and period were used as fixed effects, and subjects nested within sequence were used as a random effect. The geometric least-squares mean ratios between drug regimens (CDFR0209/omeprazole-DR) and the corresponding 90% confidence intervals (CIs) were calculated.

Conventional pH-based indices (ie, median pH, percent time pH > 4 over a 24-hour period) were also calculated and compared using a Mann-Whitney *U* test.

All data analyses were performed using SPSS version 12.0 (SPSS Korea, Seoul, Republic of Korea).

Results

Study Subjects

A total of 30 healthy male subjects were enrolled, and 26 subjects completed the study in accordance with the protocol and had complete pharmacodynamic data for both treatment periods. The mean age was 25.4 years (range, 20–41 years), weight 71.6 kg, and height 176.5 cm. Overall, 4 subjects voluntarily withdrew consent for personal reasons.

Pharmacodynamics

The 24-hour intragastric pH (mean pH per hour) profiles at baseline, after the first dose (day 1), and after the seventh dose (day 7) of CDFR0209 or omeprazole-DR are presented in Figure 1. During the baseline period, the 24-hour intragastric pH fluctuated within a range of approximately pH 1–3, and sharp increases in pH were observed 5 and 11 hours after a meal, followed by gradual decreases. Following the first dose of CDFR0209 or omeprazole-DR on day 1, the intragastric pH increased up to pH 4 around 2 hours after CDFR0209 and 3 hours after omeprazole-DR. On day 7, the 24-hour intragastric pH–time profiles were much higher than at baseline or on day 1 and increased to a maximum pH of 6 around 2 hours after CDFR0209 and 3 hours after omeprazole-DR.

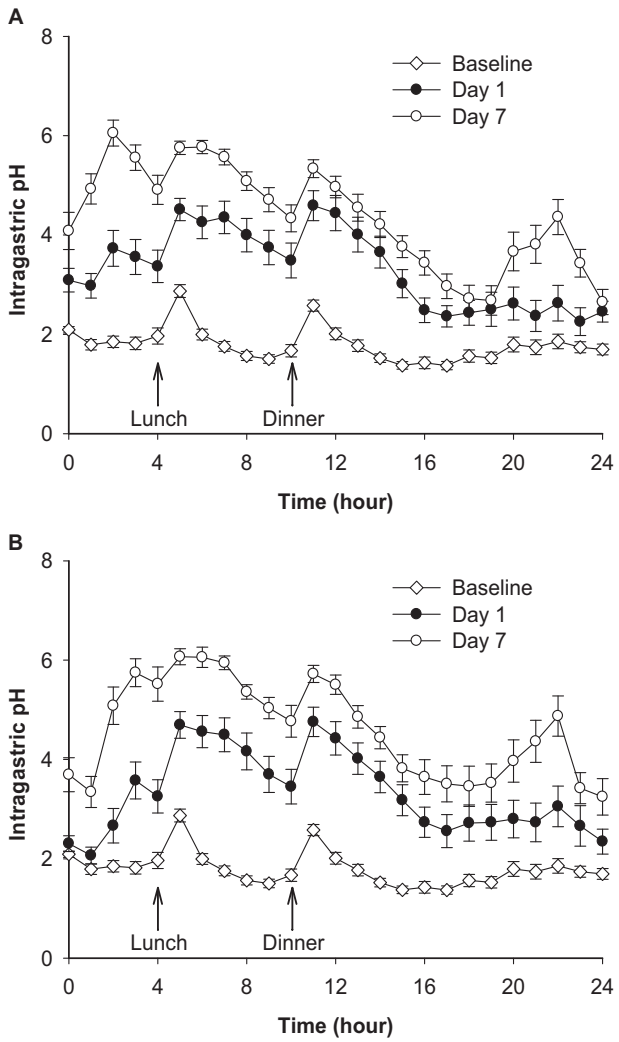

Figure 1. Mean (SE) intragastric pH with CDFR0209 (A) and omeprazole-DR (B) at the baseline, on days 1 and 7 in healthy adult male subjects.

Figure 2 illustrates values for mean integrated gastric acidity after the first and seventh doses of CDFR0209 or omeprazole-DR. In both groups, the first dose of the study drug caused a significant decrease in the integrated gastric acidity, and integrated

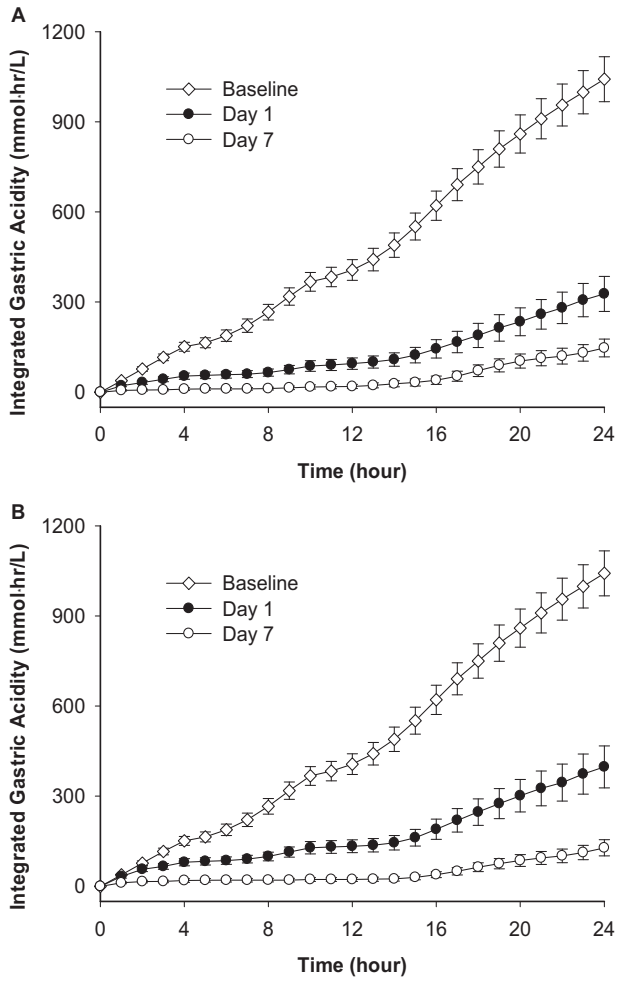

Figure 2. Cumulative integrated gastric acidity with CDFR0209 (A) and omeprazole-DR (B) at the baseline, on days 1 and 7 in healthy adult male subjects.

gastric acidity was decreased further after the seventh dose of the study drug. Mean ± standard deviation percent decrease from the baseline in integrated gastric acidity of CDFR0209 and omeprazole-DR on day 1 was 65.5% ± 33.0% and 62.7% ± 31.3%, respectively, and on day 7 was 84.4% ± 14.9% and 86.5% ± 14.6%, respectively. The geometric least-squares mean ratios (CDFR0209/omeprazole-DR) of percent decrease from the baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation was 0.98 (90%CI, 0.93–1.07); see Table 1.

There were no statistically significant differences in intragastric pH values on day 7 between CDFR0209 and omeprazole-DR (Table 2). Over the 24-hour period after the seventh dose of the study drug, the mean percentage of time with intragastric pH > 4 was 58.5% for CDFR0209 compared with 62.6% for omeprazole-DR ($P = .481$).

Safety

No serious adverse event occurred during the study. In all, 3 adverse events were reported in the CDFR0209 group (2 episodes of urticaria and 1 episode of indigestion), and 1 adverse event was reported in the omeprazole-DR group (1 episode of urticaria). All adverse events were of mild severity, and all resolved without therapy. No clinically significant changes were observed in the clinical laboratory test results or on physical examination.

Discussion

PPIs are the drug of choice for the treatment of gastric ulcer, duodenal ulcer, and gastroesophageal reflux disease.[6,7] However, as PPIs are acid labile, they need to be protected from the destructive effects of gastric acid after oral administration. Various types of enteric coatings have been developed to protect the PPIs, but they all delay absorption of the PPI. To overcome this limitation, an immediate-release formulation of omeprazole (CDFR0209) was developed by combining omeprazole with sodium bicarbonate. The bicarbonate raises the pH of the stomach, protects the omeprazole, and allows it to pass safely to the duodenum, where it is absorbed.

We compared the acid inhibitory effects of CDFR0209 and omeprazole-DR after repeated dosing in *Helicobacter pylori*–negative healthy adult male subjects. CDFR0209 and omeprazole-DR showed similar pharmacodynamic profiles, and the 90%CIs of the percent decrease from the baseline in integrated gastric acidity for the 24-hour interval after the seventh-dose ratios fell within the acceptance range of 80%–125%, indicating that CDFR0209 and omeprazole-DR were equivalent with respect to the acid inhibitory effect. CDFR0209 and omeprazole-DR

Table 1. Mean (SD) Percent Decrease From Baseline in 24-Hour Integrated Gastric Acidity After First and Seventh Doses of CDFR0209 and Omeprazole-DR in Health Adult Male Subjects

	CDFR0209	Omeprazole-DR	Geometric Mean Ratio, CDFR0209/Omeprazole-DR (90%CI)
Day 1	65.5 (33.0)	62.7 (31.3)	1.39 (0.79–2.45)
Day 7	84.4 (14.9)	86.5 (14.6)	0.98 (0.93–1.07)

CI, confidence interval.

Table 2. Intragastric pH After the Seventh Dose of CDFR0209 and Omeprazole-DR in Healthy Adult Male Subjects

	CDFR0209	Omeprazole-DR	*P*
Median pH (range)			
24-Hour	4.6 (1.8–6.4)	4.9 (2.2–7.7)	.351
Upright[a]	5.1 (2.4–6.2)	5.3 (3.4–7.8)	.601
Supine[b]	2.9 (1.4–6.9)	3.5 (1.5–7.6)	.365
Mean percentage of time with pH > 4 (SD)			
24-Hour	58.5 (16.7)	62.6 (18.7)	.481
Upright	71.1 (15.8)	72.4 (16.6)	.838
Supine	33.3 (24.4)	43.0 (29.1)	.293

[a]pH between 6 AM and 10 PM.
[b]pH between 10 PM and 6 AM of the following day.

were also shown to have a similar median pH and a mean percentage of time, with pH > 4 after the seventh dose. Overall, acid inhibitory effects were similar, with CDFR0209 resulting in rapid elevation of gastric pH greater than that of omeprazole-DR.

In this study, only *Helicobacter pylori*–negative subjects were enrolled because in *Helicobacter pylori*–positive subjects the acid inhibitory efficacies of PPIs are generally higher than those in *Helicobacter pylori*–negative subjects.[8,9] Individuals with both a negative UBT and a negative serological test (IgG) were considered free from *Helicobacter pylori* infection. The combination of the 2 methods might improve the accuracy of *Helicobacter pylori* detection.

PPI inhibits the gastric H^+,K^+-ATPase by covalent bonding at cysteines near the ion pathway.[10] Because of the properties of covalent bonds, their inhibitory effects last much longer than their plasma half-life. Therefore, the duration of the effect on H^+,K^+-ATPase because of omeprazole rather than the plasma half-life of omeprazole was considered when the washout period was determined.

Genetic polymorphism of cytochrome P450 2C19 (CYP2C19) has been reported to affect the pharmacokinetics and pharmacodynamics of omeprazole,[11,12] and the frequency of CYP2C19 poor metabolizer is approximately 12.5% in the Korean population.[13] Therefore, intragastric pH after a single dose of omeprazole may be affected by the CYP2C19 genotype status and showed higher variability in acid-suppressive indices on day 1.

The results of this study are limited by including only healthy adult male volunteers. Therefore, the study results cannot be generalized to female, elderly, or *Helicobacter pylori*–positive populations. Further comparative studies are required to determine clinical efficacy, in terms of symptom control and rate of healing, of CDFR0209 in acid-related disease.

Based on the results of this study in healthy adult male subjects, the new combination of immediate-release formulation of omeprazole 40 mg and sodium bicarbonate 1100 mg (CDFR0209) and omeprazole-DR was comparable with regard to pharmacodynamic characteristics and safety profiles.

Declaration of Conflicting Interests

Hyunil Kim and Seong Shin Kwak are full-time employees of Product Development Division, CTCBIO Inc.

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