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Original Article

A Randomized, Double-Blind, Active-Control, Noninferiority, Multicenter, Phase 4 Study to Evaluate the Efficacy and Safety of Esomeprazole/Sodium Bicarbonate 20/800 mg in Patients with Nonerosive Gastroesophageal Reflux Disease

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Background/Aims: Efficacy of proton pump inhibitors is limited in patients with nonerosive reflux disease (NERD). The aim of this study was to comparatively evaluate the efficacy and safety of esomeprazole with sodium bicarbonate and esomeprazole alone.

Methods: This was a multicenter, randomized, double-blind, active-controlled, noninferiority comparative study. A total of 379 patients with NERD were randomly allocated to receive either Esoduo® (esomeprazole 20 mg with sodium bicarbonate 800 mg) or Nexium® (esomeprazole 20 mg) once daily for 4 weeks from January 2019 to December 2019. The patients had a history of heartburn for at least 2 days in the week before randomization as well as in the last 3 months and no esophageal mucosal breaks on endoscopy. The primary endpoint was a complete cure of heartburn at week 4. The secondary and exploratory endpoints as well as the safety profiles were compared in the groups at weeks 2 and 4.

Results: A total of 355 patients completed the study (180 in the Esoduo® group and 175 in the Nexium® group). The proportions of patients without heartburn in the entire 4th week of treatment were not different between the two groups (33.33% in the Esoduo® group and 35% in the Nexium® group, p=0.737). There were no significant differences in most of the secondary and exploratory endpoints as well as the safety profiles.

Conclusions: Esoduo® is as effective and safe as Nexium® for managing typical symptoms in patients with NERD (ClinicalTrial.gov identifier: NCT03928470). **(Gut Liver 2023;17:226-233)**

Key Words: Gastroesophageal reflux; Phase IV clinical trial; Esomeprazole; Sodium bicarbonate

INTRODUCTION

Gastroesophageal reflux disease (GERD) manifests as symptoms such as heartburn and acid regurgitation caused by reflux of gastric contents into the esophagus.[1] GERD is one of the most common gastroenterological disorders.[2]

The prevalence of GERD is steadily increasing in Korea, accounting for 10% of the overall prevalence in Asia. Proton pump inhibitors (PPIs) are the mainstay treatment and are widely used for managing GERD symptoms. The efficacy of PPIs is greater in controlling the symptoms of GERD as well as in resolving esophageal erosions than that of other anti-secretory agents such as histamine receptor 2 antagonists as well as placebo.[3-5] However, the efficacy of PPIs is poor in patients with nonerosive reflux disease (NERD) who have no definite esophageal mucosal breaks on endoscopy.[4,6] Studies demonstrate that an inadequate response to PPIs is 10% to 20% greater in patients with NERD than those with erosive esophagitis (inadequate response rate, 20% to 30%).[4,5] Nevertheless, PPIs still remain the mainstay treatment for NERD.[7]

The PPIs being currently used are omeprazole, rabeprazole, esomeprazole, pantoprazole, and lansoprazole. All these PPIs have the same mechanism of action: a strong effect on gastric acid secretion by blocking the H^+-K^+ ATPase in the canaliculi of meal-activated proton pumps.[8] They do not significantly differ in terms of efficacy and safety, although there are differences in their pKa and a more favorable efficacy of specific PPIs such as esomeprazole in severe esophagitis.[9] In addition, they need enteric coating because of vulnerability to gastric acid-mediated degradation, and thus, are slowly absorbed, resulting in delayed effectiveness.[10-12] In order to overcome this delayed effectiveness due to slow absorption, PPIs can be combined to sodium bicarbonate, an antacid able to neutralize acid and increase the gastric pH, which prevents gastric acid-mediated degradation. One example is an immediate-release (IR) formulation containing 20 mg of esomeprazole and 800 mg of sodium bicarbonate (Esoduo®; Chong Kun Dang Pharmaceutical Corp., Seoul, Korea). As a result of no need of enteric coating, it is quickly absorbed in the proximal small intestine and becomes effective fast. In a study of healthy men, IR esomeprazole showed rapid, safe, and sustained suppression of gastric acid.[13] Moreover, previous clinical trials in patients with GERD have demonstrated that IR PPIs are more effective and safe than other delayed-release (DR) PPIs concerning nocturnal acid breakthrough (NAB) and pharmacokinetic advantages.[14,15]

However, whether IR PPIs are effective and safe in patients with NERD has not been established. Therefore, this multicenter, randomized, double-blind, active-control, phase 4 clinical trial was conducted to evaluate the efficacy and safety of Esoduo® by determining the cure rate of heartburn in patients with NERD after 4 weeks of Esoduo® or Nexium® treatment. Additional data analysis was performed to confirm whether symptom improvement in patients with NERD was faster in the Esoduo® group than in the Nexium® group.

MATERIALS AND METHODS

1. Study design

This was a multicenter, randomized, double-blind, active-controlled phase 4 study. The study was conducted at 38 Korean hospitals from January 2019 to December 2019 (ClinicalTrial.gov identifier: NCT03928470). The study protocol was reviewed and approved by the institutional review board of each hospital including Hanyang University College of Medicine (IRB number: 2018-11-026), per the ethical principles of the Declaration of Helsinki and Good Clinical Practice. All participants agreed to sign the informed consent form before enrollment.

Patients with heartburn were voluntarily recruited through either outpatient visits or poster advertisements at each institution. Following a screening period of 0 to 1 week, eligible patients were randomly assigned to receive the study drug (Esoduo®: esomeprazole 20 mg and sodium bicarbonate 800 mg) or the control drug (Nexium®: esomeprazole 20 mg) once daily. Treatments were assigned by a computer-generated randomization schedule to allocate patients to the two treatment arms in a 1:1 ratio. Sequential allocation numbers were assigned to the patients at each center. To maintain double-blind conditions, patients took tablets identical in appearance in the morning before breakfast (2 pills of Esoduo® + Nexium® placebo or Nexium® + Esoduo® placebo, respectively).

2. Patients

The enrolled subjects included male and female patients aged more than 19 years who had a history of heartburn in the 3 months or more and an episode of heartburn for 2 days or more in the week before randomization visit and had no esophageal mucosal breaks on endoscopy at the time of or within 3 weeks before enrollment. The exclusion criteria were as follows: active peptic ulcer disease; Barrett's esophagus (>3 cm); esophageal stricture; achalasia; eosinophilic esophagitis; esophageal diverticulum; primary motility disorder; irritable bowel syndrome; pancreato-biliary disorder; malabsorption; Zollinger-Ellison syndrome; previous gastric or major gastrointestinal surgery (except primary closure of ulcer perforation); malignancy within 5 years; significant morbidity of the heart, kidney, liver, or lung; neuropsychiatric disorder; uncontrolled diabetes mellitus; clinically significant scleroderma; known hypersensitivities to benzimidazole or any component of the study drug; or history of taking atazanavir, nelfinavir, and rilpivirine-containing agents or any forbidden medications

(including prokinetics, mucosal protectants, antacids, histamine 2 receptor antagonists, and PPI) within 14 days or any other clinical trial medications within 28 days from the start date of the study medication. Also excluded were patients with abnormal alanine aminotransferase or alkaline phosphatase (>2 times the upper limits of normal) levels; patients who were unavailable for endoscopy; pregnant, lactating, or fertile women who did not consent to using permitted contraceptive methods, or those with any other conditions regarded unsuitable by the investigator.

3. Study assessments

1) Efficacy

The primary outcome measure was the complete resolution of heartburn at week 4, i.e., the last 7 days of treatment. Complete resolution was defined as the absence of heartburn on each day (all daytime/night-time) in the 4th week of treatment, based on the patients' symptom diaries. Heartburn was defined as a burning sensation or pain in the retrosternal area, and acid regurgitation, as bitter or acid taste because of regurgitation of gastric contents (acids or foods). Patients' symptom diary included symptom questionnaires developed for this study. Patients were instructed to keep their symptom diary and to write down their symptom severities of heartburn and regurgitation every day before bed and after waking up in the morning. Also, the severity of patients' symptoms for the last 7 days was evaluated by investigators at enrollment and after 4-week treatment.

Symptom severity in the daytime was assessed as none, no symptoms; mild, easily tolerated and not long-lasting symptoms; moderate, discomforting symptoms to slightly limit daily activities; severe, frequent symptoms to significantly limit daily activities; and very severe, sustained symptoms to severely and persistently limit daily activities. Night-time symptom severity was assessed as none, no symptoms; mild, symptoms without disturbing sleep; moderate, symptoms discomforting enough to slightly disturb sleep; severe, frequent symptoms to frequently disturb sleep; and very severe, sustained symptoms causing difficulty in sleeping.

The secondary outcome measures were as follows: (1) proportion of patients with complete resolution of heartburn at week 2 after treatment; (2) proportion of patients with complete resolution of acid regurgitation at weeks 2 and 4 after treatment; (3) proportion of patients who had symptoms of heartburn or acid regurgitation for only 1 day or less at weeks 2 and 4 after treatment; (4) proportions of days without symptoms of heartburn/acid regurgitation at weeks 2 and 4 after treatment; (5) the time to the first 24/48 hours without heartburn/acid regurgitation; (6) changes in symptom scores of heartburn/acid regurgitation from baseline at weeks 2 and 4 after treatment; and (7) investigator assessment of heartburn/acid regurgitation at week 4 after treatment.

The exploratory endpoint was the time to the first resolution of heartburn on the first day to evaluate the rapidity of the effectiveness of the study drug.

2) Safety

The safety of the study drugs and the drug compliance were evaluated based on all adverse events reported by the patients, physical examination results, and laboratory test findings at weeks 2 and 4 after randomization. Adverse drug reaction refers to any unintended adverse reaction that occurs at any dose of the investigational drugs, and their causal relationship cannot be denied. Drug compliance was defined as good when it was more than or equal to 80.0% and less than or equal to 120.0%. The safety set included all patients who took the study drug at least once after randomization and underwent follow-up for safety evaluation.

4. Sample size and statistical analysis

The required sample size was estimated in a previous study that reported that the cure rates of heartburn at week 4 were 41.4% and 11.2% in the Nexium® and placebo groups, respectively. Thus, the margin of noninferiority was assumed to be 15%, approximately half of 30.2%, the difference between the two groups. To have a power of 80% and α of 0.05 while allowing for a 10% drop-out rate, a total of 378 patients were needed (189 per group). The test group was considered non-inferior to the control group when the upper limit of the 95% confidence interval was less than 0.15, based on the chi-square test performed for comparing the proportions of patients with complete resolution between the Esoduo® and Nexium® groups.

The demographic and baseline characteristics of all patients included in the full analysis set (FAS) were analyzed. All the efficacy variables were analyzed based on the FAS and per-protocol set (PPS). The FAS consisted of all randomized patients who received at least one dose of the study drug and underwent at least one post-baseline efficacy assessment. The PPS included all patients in the FAS population who took more than or equal to 80% and less than or equal to 120% of their assigned drugs and violated no major protocol. The safety set included all patients who received at least one dose of the study drug and underwent a follow-up assessment.

Data were analyzed by two-tailed tests with significance set at $p < 0.05$ using SAS version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables are presented as num-

bers and mean, standard deviation, minimum, median, and maximum values. After normality testing, continuous variables were analyzed using paired t-tests or Wilcoxon signed-rank tests for in-group comparisons and two-sample t-tests or Wilcoxon rank-sum tests for intergroup comparisons. Categorical variables were presented as numbers and proportions and were analyzed using Pearson chi-square or Fisher exact tests for intergroup comparisons.

RESULTS

1. Allocation of patients

A total of 421 patients were screened at the 38 centers involved in the study. After excluding 42 patients during screening, the remaining 379 patients were randomized to treatment: 190 and 189 in the Esoduo® and Nexium® groups, respectively (Fig. 1). Two patients who did not take the control drug were excluded from the safety set. Eleven patients without efficacy measurements as well as additional two patients (not taking the study drugs) were excluded from the FAS. Thus, 366 patients (186 in the Esoduo® group and 180 in the Nexium® group) were included in the FAS; included in the PPS were 343 patients (173 in the Esoduo® group and 170 in the Nexium® group) of 355 patients who completed the study.

2. Demographics and clinical characteristics

The demographic and baseline characteristics of the subjects were well balanced for sex, age, and symptom severity at baseline (Table 1).

3. Primary efficacy assessments

The proportions of patients without heartburn in the entire 4th week of treatment were not significantly different between the two groups (33.33% in the Esoduo® group and 35% in the Nexium® group, p=0.737) (Table 2). The 95% confidence interval for the difference between the groups was in the range of –0.0805 to 0.1139, indicating that the upper limit was lower than 0.15, which means that the Esoduo® group was not inferior to the Nexium® group. The results for the FAS and PPS were similar.

In additional analysis of the primary outcome, when compared in patients with complete resolution of heartburn at week 4, there were more patients who had daytime heartburn for more than 3 days in the Esoduo® group than Nexium® group (27.4% vs 12.7%, p=0.040) (Table 3).

4. Secondary efficacy assessment

Most of the secondary endpoints were not significantly different between the groups. We found no significant differences between the groups in the proportions of patients without heartburn at week 2 (22.0% in the Esoduo® and 21.1% in the Nexium® group) (Table 2), those without symptoms of acid regurgitation at week 2 (37.1% vs 38.3%) and week 4 (49.5% vs 43.9%) (Table 4), and with symptoms of heartburn or acid regurgitation for less than 1 day in week 2 (22.0% vs 20.0%) and week 4 (34.9% vs 32.8%) (all p>0.05) (Table 4). The proportions of days without symptoms of heartburn/acid regurgitation at weeks 2 and 4 were not different. The median time to the first day without heartburn/acid regurgitation was not significantly different between the groups (7.3 days in the Esoduo® and 9.0 days

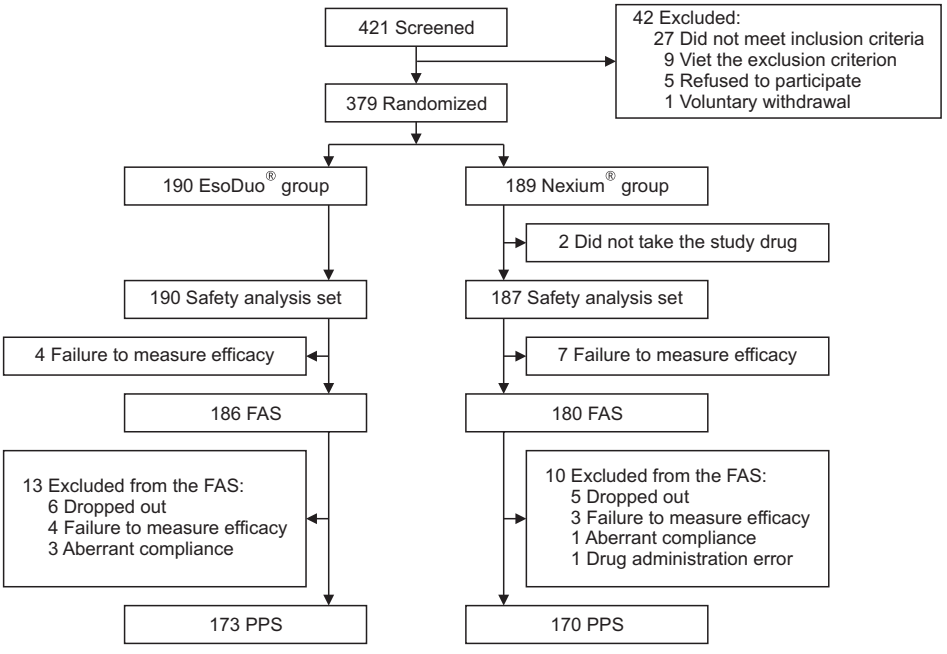

Fig. 1. Enrollment, randomization, and follow-up of patients.
FAS, full analysis set; PPS, per-protocol set.

in the Nexium® group, p=0.182). The changes in the symptom scores of heartburn/acid regurgitation from baseline at weeks 2 and 4 significantly improved with no differences between the two groups except for those pertaining to daytime acid regurgitation (Supplementary Table 1). Symptom scores in acid regurgitation during the daytime were significantly lower in the Esoduo® group than in the Nexium® group. Investigator assessment of symptom severities after 4-week treatment significantly improved in both groups (Supplementary Table 2).

We found that among the patients with more severe symptoms, the symptoms were better managed by Esoduo® than by Nexium®. In patients with heartburn and acid reflux for more than 2 days in the week before enrollment, the cure rates of symptoms at week 2 were higher in the Esoduo® group than in the Nexium® group (heartburn: 9/55 [16.4%] vs 1/44 [2.3%], p=0.039; acid reflux: 10/55 [18.2%] vs 2/44 [4.5%], p=0.039). Further, time to the resolution of heartburn after treatment at day 1 tended to be shorter in the Esoduo® than in the Nexium® group, with the intergroup difference being insignificant (168.1 minutes vs 212.7 minutes, respectively, p=0.200).

5. Safety

In analysis of the safety set including 377 patients, the two groups were not significantly different. Adverse events were mostly mild, and not different between the two groups. No serious adverse events were reported in either group. A total of 43 mild, four moderate, and three severe

Table 1. Demographic Characteristics of Subjects with Nonerosive Esophageal Reflux Disease

Variable	Esoduo® group (n=186)	Nexium® group (n=180)	p-value
Female sex	122 (65.6)	123 (68.3)	0.577*
Age, yr	47.24±15.34	46.17±14.31	0.505†
Childbearing potential	68 (55.7)	69 (56.1)	0.955*
Negative urine pregnancy test	67 (100.0)	69 (100.0)	-
Body mass index, kg/m^2	23.20±2.92	23.25±3.37	0.728†
Symptom duration, yr	1.23±3.31	1.48±3.25	0.865†

Data are presented as the number (%) or mean±SD.
*Chi-square test for intergroup comparison; †Wilcoxon rank-sum test for intergroup comparison of mean values.

Table 2. Proportions of Patients with Complete Resolution of Heartburn at Weeks 2 and 4 after Treatment (Full Analysis Set)

Complete resolution of heartburn	Esoduo® group (n=186)	Nexium® group (n=180)	p-value†
Week 2	41 (22.04)	38 (21.11)	0.829
Week 4*	62 (33.33)	63 (35.00)	0.737

Data are presented as the number (%).
*The proportions of patients without heartburn (both daytime and night-time) in the entire 4th week of treatment were not different between the groups. The 95% confidence interval for the difference between the groups was in the range of –0.0805 to 0.1139, indicating that the upper limit was lower than 0.15, which means that the Esoduo® group was not inferior to the Nexium® group; †Chi-square test for intergroup comparison.

Table 3. Proportions of Patients with Symptoms for More Than 3 Days among Those Patients with Complete Resolution of Heartburn at Week 4

Variable	Total (n=125)	Esoduo® group (n=62)	Nexium® group (n=63)	p-value*
Heartburn				
Daytime (>3 days)	25 (20.0)	17 (27.4)	8 (12.7)	0.040
Night-time (>3 days)	18 (14.4)	10 (16.1)	8 (12.7)	0.585
Acid regurgitation				
Daytime (>3 days)	21 (16.8)	12 (19.4)	9 (14.3)	0.449
Night-time (>3 days)	14 (11.2)	7 (11.3)	7 (11.1)	0.975

Data are presented as the number (%).
*Chi-square test for intergroup comparison.

Table 4. Treatment Responses of the Study Patients at Weeks 2 and 4

Variable	Esoduo® group (n=186)	Nexium® group (n=180)	p-value*
Subjects who had no symptoms of acid regurgitation			
Week 2	69 (37.1)	69 (38.3)	0.807
Week 4	92 (49.5)	79 (43.9)	0.285
Subjects who had symptoms of heartburn/acid regurgitation only for ≤1 day			
Week 2	41 (22.0)	36 (20.0)	0.632
Week 4	65 (34.9)	59 (32.8)	0.661

Data are presented as the number (%).
*Chi-square test for comparison of the proportions between the groups.

Table 5. Adverse Drug Reactions during the Study (Safety Set)

Events	Esoduo® group (n=190)	Nexium® group (n=187)	p-value*
Total	3 (1.6)	4 (2.1)	0.722
Gastrointestinal disorders	3 (1.6)	3 (1.6)	1.000
Diarrhea	2 (1.1)	-	0.499
Nausea	-	2 (1.1)	0.245
Constipation	-	1 (0.5)	0.496
Dyspepsia	1 (0.5)	-	1.000
Oral paresthesia	-	1 (0.5)	0.496
Infections and infestations	-	1 (0.5)	0.496
Pharyngitis	-	1 (0.5)	0.496
Nervous system disorders	-	1 (0.5)	0.496
Dizziness	-	1 (0.5)	0.496

Data are presented as the number (%).
*Fisher exact test for comparison of proportions between groups.

adverse events were observed. Three and four adverse drug reactions were noted in the Esoduo® and Nexium® groups, respectively (Table 5). Changes in laboratory test results from baseline normal values were noted in four cases, and the presence of albumin in urine and blood samples was recorded as an adverse event. Although physical examinations indicated changes in the Esoduo® group, including changes in vital signs, body weight, and diastolic blood pressure, the changes were not clinically significant.

DISCUSSION

This multicenter, randomized, double-blind, active-controlled phase 4 study demonstrates that treatment with Esoduo® once daily for 4 weeks in adult patients with NERD has a non-inferior efficacy to that of the standard dose of esomeprazole once daily. In the FAS analysis, the proportion of patients with complete cure of heartburn after 4-week treatment of Esoduo® was 33.33%, which was not significantly different from that in the Nexium® group (35%, p=0.737). Furthermore, Esoduo® was not inferior to Nexium® with respect to several secondary endpoints, such as adequate symptom relief at weeks 2 and 4. Moreover, Esoduo® had a safety profile similar to that of Nexium®, with no serious adverse events or serious adverse drug reactions. In the subgroup analysis, Esoduo® was more effective and faster than Nexium® particularly for those with severe symptoms, although not statistically significant.

These results are supported by IR esomeprazole with advantageous pharmacokinetic and pharmacodynamic properties.[16] A faster onset of action of IR esomeprazole has been confirmed in previous studies that evaluated pharmacokinetic parameters such as time to peak plasma concentration after dosing, and gastric acidity parameters such as time to first reach a pH of >4 and percentage of time for which pH was >4 after dosing as well as resolution of symptoms such as NAB.[14,15] In a study of 40 healthy volunteers,[13] the time to peak plasma concentration was shorter for IR esomeprazole (esomeprazole 20 mg+sodium bicarbonate 800 mg) than for DR esomeprazole (20 mg) (0.50–0.75 hours vs 1.25–1.50 hours), which is due to rapid absorption of IR esomeprazole. Moreover, the time to first reach a pH of >4 after dosing was shorter for IR esomeprazole, indicating a rapid onset of action. These advantages can be attributable to sodium bicarbonate, which has a neutralizing effect on gastric acidity and thereby protects esomeprazole from degradation. These suggest a faster resolution of symptoms upon the use of IR esomeprazole than of DR form, although no differences were noted in the parameters of 24-hour integrated gastric acidity from baseline and the mean time to the maintenance of a gastric pH of >4 for 24 hours.[13]

A faster resolution of GERD symptoms by IR PPIs was also confirmed in studies evaluating NAB.[14,15] IR PPIs (omeprazole) was superior in reducing NAB compared to DR PPIs (lansoprazole and pantoprazole). One study identified that reporting NAB in IR omeprazole group was significantly less frequent than that in DR lansoprazole/esomeprazole group (60% vs 92%).[14] In another study comparing IR omeprazole once daily at bedtime with DR pantoprazole once daily before dinner or twice daily (before breakfast and bedtime), NAB was reported significantly less frequently in IR omeprazole group (53% vs 78% and 75%, respectively).[15] Therefore, although not shown in this study, the efficacy in terms of NAB in previous studies confirm the rapid absorption and action of IR PPIs. Obviously, this difference would be caused by the difference in study designs, such as administration at night time compared with the morning premeal administration in this study. One putative mechanism of this superiority in symptom resolution was suggested to be the absence of meal-stimulated activation of proton pumps that are supposed to be the target of PPIs. However, the antacid sodium bicarbonate contained in IR PPIs can induce gastrin secretion to activate proton pumps instead of meal-stimulated activation. These are consistent with our finding that symptoms resolved faster in the analysis of the exploratory endpoint, although not statistically significant. The analysis showed that the time to the resolution of heartburn on the first day was approximately 40 minutes shorter in the Esoduo® group than in the Nexium® group.

Moreover, IR PPI has been demonstrated to better control gastric acidity than DR PPI. Two previous studies investigated gastric acidity measured by median gastric pH and percentage of time with gastric pH of >4 along

with pharmacokinetic parameters. Regarding the median gastric pH, an increase >4 was achieved within 15 minutes of IR PPI administration, whereas not even after 5 hours of DR PPI administration.[15] In another study, IR PPI (omeprazole+sodium bicarbonate) showed a higher percentage of time for which pH was >4 and higher median gastric pH than with DR PPIs, in addition to a lower number of patients reporting NAB.[14] Furthermore, the pharmacokinetic analysis showed that the C_{max} of IR PPI was reached within 31 minutes and 68% of the Cmax after 10 minutes of drug administration.

In our study, Esoduo® seems to have higher efficacy in patients with severe symptoms. Among patients who were completely cured at week 4, there were more patients with severe symptoms in the Esoduo® group than in the Nexium® group. Additional analysis of the patients who were completely cured at week 4 showed more patients had daytime heartburn for more than 3 days in the Esoduo® group than in the Nexium® group. This result can be again explained by the IR PPI's advantage of rapid onset of action.

Regarding the dose of PPI used in the study, 20 mg of esomeprazole is adequate for patients with NERD, because the efficacy of half-dose PPIs was reported to be not different from that of standard-dose PPIs in patients with NERD, as the current recommendation suggests for patients with NERD in Korea.[17] As patients with NERD are usually recommended to use on demand PPIs rather than continuous half-dose PPIs, future research might be needed to evaluate whether on-demand Esoduo® is more effective and safe compared with that of conventional DR PPIs. Furthermore, considering that Esoduo® is advantageous in terms of being able to be taken regardless of meal ingestion, it might be necessary to confirm that Esoduo® is comparable to other DR PPIs with no need for meal-stimulated activation of proton pumps such as dexlansoprazole. Dexlansoprazole, the R-enantiomer of lansoprazole, has a modified dual-release technique and showed superiority to placebo in terms of proportions of patients who were heartburn-free at 24 hours during the day and night, symptom severity, and health-related quality of life.[18]

There are some limitations to this study. First, only typical symptoms of NERD, i.e., heartburn and acid reflux, were evaluated to assess the drug efficacy. Neither extraesophageal symptoms such as hoarseness or chronic cough nor the quality of life associated with GERD symptoms were evaluated. Instead, typical symptoms were meticulously assessed and analyzed through the variable secondary and exploratory endpoints as well. Second, our study population could have included patients with reflux hypersensitivity or functional heartburn because we did not perform ambulatory impedance-pH monitoring, which would be hard to be performed in primary medical clinics. Third, we did not evaluate other parameters including gastric acidity or various pharmacokinetic profiles such as C_{max}. Last, although tricyclic antidepressants influence symptoms in patients with NERD, those taking tricyclic antidepressants were not excluded in the present study. Therefore, those taking tricyclic antidepressants (three and two in each group, respectively) were excluded in the PPS.

Nonetheless, this multicenter, large-scale study is the first to show the noninferiority of IR PPI to DR PPI in patients with NERD in terms of efficacy and safety. In conclusion, our results indicate that Esoduo® 20/800 mg is effective and safe for 4-week treatment of heartburn and acid regurgitation in patients with NERD, which is not inferior to esomeprazole 20 mg.

CONFLICTS OF INTEREST

The study was sponsored and conducted by Chong Kun Dang Pharmaceutical Corp.

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AUTHOR CONTRIBUTIONS

Data analysis and interpretation: S.H.P., O.Y.L., K.N.L. Drafting of the manuscript: S.H.P., K.N.L. Study design: O.Y.L. Acquisition of data in each institute: M.G.C., J.H.K., I.K.S., J.Y.J., K.S.P., H.J.C., E.Y.K., J.K.L., J.S.J., G.H.K., S.J.H., Y.C.L., S.C.C., H.S.K., T.O.K., G.H.B., Y.C.J. Critical revision of the manuscript for important intellectual content: all authors. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220023.

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