Clinical Trials Study

First-week clinical responses to dexlansoprazole 60 mg and esomeprazole 40 mg for the treatment of grades A and B gastroesophageal reflux disease

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Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder worldwide. GERD continues to increase in incidence with the aging population and the obesity epidemic[1,2]. Based on the Montreal definition, GERD is diagnosed when the reflux of stomach contents causes troublesome symptoms[3], such as heartburn and regurgitation, as well as other atypical or extraesophageal symptoms, such as chest pain, asthma, voice hoarseness, and sleep disturbance[4]. Proton pump inhibitors (PPIs) are widely recognized as superior to other antisecretory therapies, including histamine-2 receptor antagonists (H2RA), and thus play a critical role in pharmacological therapy for the treatment of GERD[5]. Although PPIs represent the mainstay of treatment for healing erosive esophagitis,
symptom relief, and preventing complications, several studies have shown that up to 40% of GERD patients report either a partial or a complete lack of response of their symptoms after taking a standard once-daily PPI dose\textsuperscript{[6-8]}.

A study comparing the pharmacokinetic effects of different PPIs 12-24 h post-dose showed that the mean percentage of time with a pH $> 4$ and the average of the pH mean were greater for dexlansoprazole than for esomeprazole (60\% vs 42\%, $P < 0.001$ and pH 4.5 vs 3.5, $P < 0.001$). However, this study did not report the clinical effects after the use of tablets\textsuperscript{[9]}.

Rapid onset PPIs for fast symptom relief is an unmet need in GERD treatment. To date, no reports have investigated the differences in short-term clinical effects and timing to symptom relief of GERD between dexlansoprazole 60 mg and esomeprazole 40 mg. Therefore, we conducted a randomized, controlled, open-label study to compare the 7-d clinical effects of single doses of dexlansoprazole (60 mg) and esomeprazole (40 mg) in patients with Los Angeles (LA) grades A and B erosive esophagitis.

**MATERIALS AND METHODS**

**Ethics statement**

This study was funded by the Research Foundation of the Chang Gung Memorial Hospital, Taiwan (CMRPBGD1441). This open-labeled trial was conducted at Kaoshiung Chang Gung Memorial Hospital, Kaohsiung Medical University Hospital, and Kaohsiung Veterans General Hospital in Taiwan. The study protocol was approved by the Ethics Committees of the above three hospitals. All patients provided written informed consent prior to participation. This clinical trial has been registered in a publicly accessible registry (ClinicalTrials.gov number: NCT03128736).

**Study population**

We invited 243 eligible outpatients to join our study. The outpatients were at least 18 years old, presented with clinical symptoms of acid regurgitation, heartburn, and a feeling of acidity in the stomach\textsuperscript{[10]}, and had endoscopy-confirmed LA grade A or B erosive esophagitis\textsuperscript{[11,12]}. We enrolled a total of 175 patients using strict inclusion criteria. The exclusion criteria included (1) those who had been taking antisecretory agents, such as PPIs and H$_2$RA, within 2 wk prior to the endoscopy; (2) those who had coexistence of a peptic ulcer or gastrointestinal malignancies, and were pregnant; (3) those who had coexistence of a serious concomitant illness (e.g., decompensated liver cirrhosis and uremia); (4) those who underwent previous gastric surgery; (5) those who were allergic to dexlansoprazole or esomeprazole; and (6) those who had a symptom score less than 12 on a validated questionnaire (Chinese GERDQ)\textsuperscript{[10]}.

**Study protocol**

Figure 1 shows the schematic flowchart of the study design. Eligible patients were randomly assigned to receive either dexlansoprazole 60 mg q.d. or esomeprazole 40 mg q.d. for 8 wk as an initial treatment. Randomization was conducted using a computer-generated list of random numbers in a 1:1 ratio into two sequence groups that defined the order in which the patients received a single dose of dexlansoprazole or esomeprazole for an intention-to-treat analysis. An independent staff member assigned the treatments according to consecutive numbers kept in sealed envelopes. Written informed consent was obtained from each patient.

Each patient completed diary cards during the study period. Complete symptom resolution (CSR) was defined as no reflux symptoms leading to troublesome feelings in the 7 d of initial treatment. The patients were asked to complete the Chinese GERDQ upon recruitment\textsuperscript{[10]}. The selected symptoms that best accounted for the differences between the
patients with GERD and the controls included acid regurgitation, heartburn, and a feeling of acidity in the stomach. The severity and frequency of symptoms in the questionnaire were graded on a five-point Likert scale as follows: (1) none; no symptoms/none in the last month); (2) mild: symptoms could be easily ignored/less than once per month); (3) (moderate: awareness of symptoms but easily tolerated/≥ once per month); (4) (severe: symptoms sufficient to interfere with normal activities/≥ once per week); and (5) (incapacitating: incapacitating symptoms with an inability to perform daily activities or requiring a day off work/≥ once daily) [10]. Blood samples were collected to measure the fasting blood sugar, serum cholesterol, and triglyceride levels. In addition, the body mass index (BMI) was calculated. Upon initial endoscopy, specimens taken from the greater curvature within 5 cm from the pylorus and from the greater curvature of the middle body were subjected to a microscopic examination for Helicobacter pylori (H. pylori) using a hematoxylin and eosin stain. No eradication therapy was administered during the study period.

Patient demographic data and follow-up
A complete medical history and demographic data were obtained from each patient. The collected variables included age (< 60 or ≥ 60 years), sex, history of smoking, history of alcohol consumption (< 80 g/d or ≥ 80 g/d), coffee ingestion (< 1 cup/d or ≥ 1 cup/d), tea ingestion (< 1 cup/d or ≥ 1 cup/d), coexistence of a systemic disease (yes or no), severity of erosive esophagitis, and BMI. A gastric biopsy for histology and an H. pylori examination were also performed. The patients returned to the clinics for drug refills and evaluation of reflux symptoms after one week. Adverse events were prospectively evaluated. The adverse events were assessed according to a 4-point scale system as follows: none; mild (discomfort, annoying but not interfering with daily work); moderate (discomfort sufficient to interfere with daily work); and severe (discomfort resulting in discontinuation of PPI therapy). Compliance was checked by counting the unused medication at the completion of 7 d of treatment.

End points
CSR was defined as no reflux symptoms sufficient to impair the quality of life before the end of the initial treatment phase. The main outcome measures were the CSR rates at days 1, 3 and 7 of the initial treatment period. All patients who started esomeprazole or dexlansoprazole as their initial treatment were included in the intent-to-treat (ITT) analysis. Patients with poor drug compliance were excluded from the per-protocol (PP) analysis. Poor compliance was defined as taking less than 80% of the total medication during the initial treatment phase.

Statistical analysis
According to the observations in this study, the CSR rate after a once-daily PPI therapy was approximately 50% at day 7. Assuming that the two types of PPIs provided similar effects on the CSR rates with a standard deviation of less than 10% [13], we estimated that we required at least 196 patients in each treatment group to demonstrate a 10% absolute difference in the CSR with a type I error of 0.05 and a statistical power of 80% and assuming a 10% loss to follow-up. As a consequence of not achieving the target number, our study was a pilot study.

In this pilot study, the χ² test with or without Yates correction for continuity and Fisher’s exact test were used when appropriate to compare the rates of CSR, symptom relapse, and esophagitis relapse between the groups. The mean reflux symptom scores between groups were compared using the Wilcoxon rank sum test. All statistical analyses were performed using the SPSS program (version 10.1, Chicago, IL, United States). A P value less than 0.05 was considered significant.

RESULTS
From April 2014 to March 2016, two hundred and forty-three eligible symptomatic patients who had endoscopy-confirmed Los Angeles grade A or B erosive esophagitis were assessed. A total of 175 of these patients were recruited for randomization after excluding 68 patients who refused enrollment (n = 40), cancer patients (n = 19), and patients with advanced liver disease (n = 3), end-stage renal disease (n = 4), and coronary heart disease (n = 2). A total of 88 patients received the dexlansoprazole treatment, and 87 patients received the esomeprazole treatment. A total of 13 patients were lost during the follow-up period (seven in the dexlansoprazole group and 6 in the esomeprazole group) (Figure 1). The baseline characteristics of the two groups were similar in age, sex, diet habits, body mass index, and symptom scores (GERDQ) (Table 1). At days 1, 3, and 7 post-dose, the CSR rates for the dexlansoprazole vs esomeprazole groups were 25.9% vs 28.4% (P = 0.724), 33.3% vs 32.1% (P = 0.867), and 51.9% vs 48.1% (P = 0.637), respectively. The symptoms and frequencies of nighttime reflux were similar in both groups (Table 2). In the subgroup analysis based on sex, females had higher CSR rates in the dexlansoprazole group at day 3 (38.3% vs 18.4%, P = 0.046), and an increasing trend was observed at day 7 (55.3% vs 36.8%, P = 0.09) (Table 3). However, no significant differences were observed in the subgroup analyses based on age and body weight. After splitting
the data from the two PPI groups in the multivariate analysis, no dependent factor for CSR was found in the dexlansoprazole group (Table 4). In the esomeprazole group, female sex was a negative predictive factor for CSR at post-dose days 1 [OR = -1.249 ± 0.543; 95%CI: 0.287 (0.099-0.832), P = 0.022] and 3 [OR = -1.254 ± 0.519; 95%CI: 0.285 (0.103-0.789), P = 0.016] in the esomeprazole group. We also found a decreasing trend in CSR rates at day 3 (55.3% vs 42.0%, OR = 0.64, 95% CI: 0.43-0.95, P = 0.027) and day 7 (36.8% vs 21.4%, OR = 0.50, 95% CI: 0.30-0.83, P = 0.01) in the esomeprazole group.

**DISCUSSION**

We conducted a randomized, controlled, open-label study to compare the 7-d clinical effects of single doses of dexlansoprazole 60 mg and esomeprazole 40 mg for GERD patients. We observed that the overall CSR rates for GERD patients were similar at days 1 through 7 of treatment for both the dexlansoprazole and esomeprazole groups. However, in our subgroup analysis based on sex, we observed that females had higher CSR rates in the dexlansoprazole group at day 3 (38.3% vs 18.4%, P = 0.046), and an increasing trend was observed at day 7 (55.3% vs 36.8%, P = 0.09). The logistic regression analysis showed that female sex was a negative predictive factor for CSR on post-dose days 1 [OR = -1.249 ± 0.543; 95%CI: 0.287 (0.099-0.832), P = 0.022] and 3 [OR = -1.254 ± 0.519; 95%CI: 0.285 (0.103-0.789), P = 0.016] in the esomeprazole group. We also found

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### Table 1 Baseline characteristics of the patients [n = 81, n (%)]

| Variables                        | Dexlansoprazole | Esomeprazole | P value  |
|----------------------------------|-----------------|--------------|----------|
| Age (mean ± SD, yr)              | 50.6 ± 13.3     | 49.9 ± 12.8  | 0.985    |
| Male sex                         | 34 (42.0)       | 43 (53.1)    | 0.137    |
| Smoking                          | 12 (14.8)       | 9 (11.1)     | 0.483    |
| Alcohol use                      | 22 (27.2)       | 22 (27.2)    | 1.000    |
| Ingestion of coffee              | 44 (54.3)       | 36 (44.4)    | 0.209    |
| Ingestion of tea                 | 58 (71.6)       | 49 (60.5)    | 0.230    |
| Betel nut                        | 4 (4.9)         | 1 (1.2)      | 0.173    |
| Spicy food                       | 52 (64.2)       | 51 (63.0)    | 0.870    |
| Sweet food                       | 72 (88.9)       | 75 (92.6)    | 0.416    |
| Body mass index                  | 25.4 ± 4.8      | 24.9 ± 4.4   | 0.420    |
| Waist girth                      | 88.8 ± 12.2     | 88.7 ± 11.4  | 0.361    |
| Metabolic syndrome               | 36 (44.4)       | 38 (46.9)    | 0.950    |
| Atypical symptoms                |                 |              |          |
| Chest pain                       | 38 (46.9)       | 39 (48.1)    | 0.588    |
| Dysphagia                        | 20 (24.7)       | 22 (27.2)    | 0.557    |
| Regurgitation of food            | 29 (35.8)       | 31 (38.3)    | 0.561    |
| Nausea                           | 26 (32.1)       | 23 (28.4)    | 0.544    |
| Hiccups                          | 37 (45.7)       | 44 (54.3)    | 0.300    |
| Foreign body sensation (throat)  | 48 (59.3)       | 40 (49.4)    | 0.301    |
| Foreign body sensation (chest)   | 16 (19.8)       | 16 (19.8)    | 0.604    |
| Hoarseness                       | 28 (34.6)       | 28 (34.6)    | 0.604    |
| Throat cleaning                  | 44 (54.3)       | 44 (54.3)    | 0.602    |
| Cough                            | 38 (46.9)       | 34 (42.0)    | 0.516    |
| Sore throat                      | 20 (24.7)       | 20 (24.7)    | 0.604    |
| Dry mouth                        | 54 (66.7)       | 52 (64.2)    | 0.590    |
| Bad breath                       | 29 (35.8)       | 30 (37.0)    | 0.590    |
| Epigastric pain                  | 36 (44.4)       | 45 (55.6)    | 0.197    |
| Epigastric fullness              | 65 (80.2)       | 54 (66.7)    | 0.111    |
| Insomnia                         | 36 (44.4)       | 28 (34.6)    | 0.199    |
| Sinusitis                        | 7 (8.6)         | 14 (17.3)    | 0.102    |
| Otitis media                     | 5 (6.2)         | 5 (6.2)      | 1.000    |
| Sugar                            | 97.4 ± 12.5     | 97.0 ± 12.8  | 0.604    |
| Cholesterol                      | 205.3 ± 36.7    | 207.7 ± 35.4 | 0.971 |
| Triglyceride                     | 121.9 ± 57.2    | 113.7 ± 64.7 | 0.284 |
| HDL                              | 54.7 ± 18.2     | 55.3 ± 14.4  | 0.866 |
| LDL                              | 127.0 ± 32.7    | 127.5 ± 32.8 | 0.942 |
| H. pylori infection              |                 |              |          |
| Previous history - no           | 10 (12.3)       | 15 (18.5)    | 0.553 |
| Current infection - no          | 10 (12.3)       | 12 (14.8)    | 0.703 |
| Endoscopic findings             |                 |              |          |
| Hiatal hernia                    | 10 (12.3)       | 15 (18.5)    | 0.347 |
| GEVF (grade 3 or 4)             | 7 (8.6)         | 8 (9.9)      | 0.521 |
| Esophagitis grade B             | 15 (18.5)       | 13 (16.0)    | 0.678 |

HDL: high-density lipoprotein; LDL: low-density lipoprotein; H. pylori: Helicobacter pylori; GEVF: Gastroesophageal flap valve.
that patients with the habit of eating spicy foods had lower CSR rates (37.3% vs 21.4%) on day 1 after the multivariate analysis (OR = -0.969 ± 0.438; 95%CI: 0.380 (0.161-0.896), P = 0.027).

Both dexlansoprazole and esomeprazole are potent PPIs for gastric acid suppression with excellent symptom relief for patients with GERD[14-19]. The advantage of dexlansoprazole MR (Takeda Pharmaceuticals, Osaka, Japan) is that it employs a novel approach by which its dual delayed-release (DDR) formulation prolongs the plasma concentration and ultimately extends the duration of acid suppression[14], thereby offering a twice-daily dosing effect in a one-time dose. Metz et al[15] found that patients who received a 60-mg dose of dexlansoprazole MR satisfactorily controlled heartburn (median of 91%-96% for 24-h heartburn-free days and 96%-99% for heartburn-free nights). Moreover, Sharma et al[16] reported that 92%-95% of patients were healed using dexlansoprazole MR for 8 wk. Conversely, esomeprazole (40 mg) is a delayed-release formulation with single-release characteristics that produces maximum plasma concentrations at approximately 1.6 h post-dose. Approximately 73%-75% heartburn-free days and 85%-91% heartburn-free nights were observed in patients who received 40 mg of esomeprazole for 4 wk[17-19]. In addition, esomeprazole at 40 mg/d also achieved good healing rates (87%-94.1%) for erosive esophagitis after 8 wk of treatment[18-20].

However, no direct head-to-head comparative report has investigated the short-term clinical effects or timing to symptom relief of GERD between dexlansoprazole at 60 mg and esomeprazole at 40 mg. Wu et al[21] reported an indirect comparative study that revealed that the dexlansoprazole 30 mg dose was more effective than esomeprazole at the 20 mg or 40 mg dose (RR = 2.01, 95%CI: 1.15-3.51; RR = 2.17, 95%CI: 1.39-3.38, respectively) for patients with non-erosive esophagitis at 4 wk. However, no significant differences were found in the healing rates of erosive esophagitis. A one-day comparative pH study showed that dexlansoprazole had a higher mean percentage of time with a pH > 4 than esomeprazole (58% and 48%, P = 0.003) at 0-24 h post-dose[20]. Unfortunately, differences in the clinical effects between these two PPIs were not mentioned.

In this study, we found that the symptoms and frequencies of nighttime reflux were similar between the dexlansoprazole and esomeprazole groups (P = 0.787 and P = 0.343, respectively). At days 1, 3, and 7 post-dose, the CSR rates between the two groups were similar (25.9% vs 28.4%, P = 0.724, 33.3% vs 32.1%, P = 0.867, and 51.9% vs 48.1%, P = 0.637, respectively). Nevertheless, we also observed that female patients had higher CSR rates in the dexlansoprazole group (P = 0.046) and an increasing trend for the effect on day 7 (P = 0.09) when we performed the subgroup analysis based on sex. Remarkably, our logistic regression analysis showed that female sex was a negative predictive factor for CSR on post-dose days 1 [OR = -1.249 ± 0.543; 95%CI: 0.287 (0.099-0.832), P = 0.022] and 3 [OR = -1.254 ± 0.519; 95%CI: 0.285 (0.103-0.789), P = 0.016] in the esomeprazole group. These findings implied that esomeprazole at 40 mg required more time (3 d) than dexlansoprazole at 60 mg to attain CSR in females. Several possible mechanisms may underlie these observations. First, both esomeprazole and dexlansoprazole are extensively metabolized in the liver by oxidation, reduction, and subsequent conversion of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP)

### Table 2  Comparison of the complete symptom resolution rates and night-time breakthrough heartburn between dexlansoprazole and esomeprazole over one week [n = 81, n (%)]

| Variables                  | Dexlansoprazole | Esomeprazole | P value |
|---------------------------|-----------------|--------------|---------|
| CSR Day 1                 | 21 (25.9)       | 23 (28.4)    | 0.724   |
| CSR Day 3                 | 27 (33.3)       | 26 (32.1)    | 0.867   |
| CSR Day 7                 | 42 (51.9)       | 39 (48.1)    | 0.637   |
| Night reflux              | 45 (76.3)       | 40 (74.1)    | 0.787   |
| Night heart burn          | 20 (33.9)       | 18 (33.3)    | 0.949   |
| Night acid reflux         | 20 (33.9)       | 19 (35.2)    | 0.886   |
| Frequency of night symptoms | 2.7 ± 2.0     | 2.7 ± 2.4    | 0.343   |

CSR: Complete symptom resolution.

### Table 3  Comparison of the complete symptom resolution rates between dexlansoprazole and esomeprazole over one week (Subgroup analysis by gender) n (%)

| Time          | Gender | Dexlansoprazole | Esomeprazole | P value |
|---------------|--------|-----------------|--------------|---------|
| CSR Day 1     | Female | 13 (27.7)       | 6 (15.8)     | 0.192   |
|               | Male   | 8 (23.5)        | 17 (39.5)    | 0.136   |
| CSR Day 3     | Female | 18 (38.3)       | 7 (18.4)     | 0.046   |
|               | Male   | 9 (26.5)        | 19 (44.2)    | 0.109   |
| CSR Day 7     | Female | 26 (55.3)       | 14 (36.8)    | 0.090   |
|               | Male   | 16 (47.1)       | 25 (58.1)    | 0.333   |

CSR: Complete symptom resolution.
The enzyme system, mainly by CYP2C19 and CYP3A4\(^{22,23}\), in the pharmacokinetics report of esomeprazole\(^{24}\), the mean exposure (AUC) to esomeprazole increases from 4.32 \(\mu\)mol·h/L on day 1 to 11.2 \(\mu\)mol·h/L on day 5 after a 40-mg once-daily dose, indicating that the pharmacokinetics of esomeprazole are time- and dose-dependent\(^{25}\). For dexlansoprazole\(^{26,27}\), no accumulation of dexlansoprazole occurs after multiple once-daily doses of 60 mg, although the mean AUC and max concentration (Cmax) values of dexlansoprazole are slightly higher (less than 10%) on day 5 than on day 1. We validated this finding by calculating the Cmax of dexlansoprazole, which was 16 \(\mu\)mol·h/L on day 1 and 17.67 \(\mu\)mol·h/L on day 5. As a result, dexlansoprazole almost achieved the target concentration on day 1. Second, ample evidence has shown that estrogen and progestogen can enhance relaxation of the lower esophageal sphincters and induce GERD symptoms\(^{28-30}\), especially in post-menopausal women taking hormone replacement therapy (HRT)\(^{31-36}\). These hypotheses might explain why female patients taking esomeprazole needed at least 3 more days to accumulate a sufficient plasma concentration to achieve plateau levels and desirable clinical effects.

Another observation in this study was the lower CSR rates in patients with the habit of eating spicy foods in the esomeprazole group at day 1 after the multivariate analysis. No reliable data are available in the existing literature regarding the role of diet or specific foods or drinks in GERD\(^{37}\), especially in post-menopausal women taking hormone replacement therapy (HRT)\(^{31-36}\). These hypotheses might explain why female patients taking esomeprazole needed at least 3 more days to accumulate a sufficient plasma concentration to achieve plateau levels and desirable clinical effects.

In addition to the above shortcoming, this study has other limitations. First, we enrolled only patients with Los Angeles grade A or B erosive esophagitis in this study and not those with Los Angeles grade C or D erosive esophagitis or Barrett’s esophagus. As a result, the study may not represent the clinical effects of the entire GERD population. Second, this study used dietary questionnaires to estimate the frequency of consumption of different types of food. Nonetheless, this pilot study is the first important report to compare the clinical efficacy of a one-week dual delayed-release treatment with dexlansoprazole at 60 mg and esomeprazole at 40 mg for grades A and B GERD patients, since fast symptomatic relief is an important unmet need in the treatment of GERD.

In conclusion, the overall CSR rates for GERD were similar at days 1 through 7 for both the dexlansoprazole and esomeprazole groups, although a higher CSR was observed at day 3 in female patients who received a single dose of dexlansoprazole. Since rapid onset of proton-pump inhibitors for fast symptom relief is an unmet need for the treatment of GERD and no report have investigated the short-term clinical effects of dexlansoprazole 60 mg vs esomeprazole 40 mg, this finding of this pilot study is novel. Furthermore, these findings may have important implications for clinical practice when treating patients with grades A and B GERD. This issue was hampered by the small sample size.

| Time  | PPI          | Clinical factors | CSR          | Coefficient of variation | Odds ratio (95%CI) | \(P\) value |
|-------|--------------|------------------|--------------|--------------------------|--------------------|------------|
| Day 1 | Dexlansoprazole | Null             | 15.80%       | -1.249 ± 0.543           | 0.285 (0.103-0.789)| 0.022      |
| Day 3 | Dexlansoprazole | Female           | 18.40%       | -1.254 ± 0.519           | 0.287 (0.099-0.832)| 0.016      |

CSR: Complete symptom resolution; PPI: Proton pump inhibitor.

| Time  | Clinical factor | CSR       | Coefficient of variation | Odds ratio (95%CI) | \(P\) value |
|-------|-----------------|-----------|--------------------------|--------------------|------------|
| Day 1 | Spicy food      | No: 37.3%| -0.969 ± 0.438           | 0.380 (0.161-0.896)| 0.027      |
| Day 3 |                 | Yes: 21.4%|                         |                    |            |
| Day 7 |                 | Null      |                         |                    |            |

CSR: Complete symptom resolution.

Table 4  Multivariate analysis of the clinical factors predictive of complete symptom resolution within one week based on dexlansoprazole and esomeprazole administration

Table 5  Multivariate analysis of the clinical factors predictive of complete symptom resolution within one week

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size. Thus, we believe that large-scale comparative studies are necessary.

**ARTICLE HIGHLIGHTS**

**Research background**

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder worldwide and continues to increase in incidence due to the aging population and obesity epidemic. Although proton pump inhibitors (PPIs) represent the mainstay of treatment for healing erosive esophagitis, symptom relief, and preventing complications, several studies have shown that up to 40% of GERD patients report either a partial or a complete lack of response of their symptoms after taking a standard once daily PPI dose. Rapid onset proton-pump inhibitors for fast symptom relief is an unmet need for GERD treatment. To date, no reports have investigated the short-term clinical effects and timing to symptom relief of gastroesophageal reflux disease (GERD) between dexlansoprazole (60 mg) and esomeprazole (40 mg). This report is the first randomized, controlled, open-label study to compare the 7-d clinical effects of single doses of dexlansoprazole at 60 mg and esomeprazole at 40 mg for LA grades A and B erosive esophagitis.

**Research motivation**

A study comparing the pharmacokinetic effects of different PPIs 12-24 h post-dose showed that the mean percentage of time with a pH > 4 and the average of the pH mean were greater for dexlansoprazole than for esomeprazole (60% vs 42%, P = 0.001 and pH 4.5 vs 3.5, P = 0.001). However, this study did not report the clinical effects after the use of tablets. Therefore, the significance of solving these problems for future research in this field should be based on large-scale, head-to-head comparisons of these PPIs on immediate symptom relief for GERD to fulfill the unmet need in real-world treatment.

**Research objectives**

The main objectives realized in this study motivated us to conduct this randomized, controlled, open-label study that compared the 7-d clinical effects of single doses of dexlansoprazole at 60 mg and esomeprazole at 40 mg for LA grades A and B erosive esophagitis.

**Research methods**

This study was funded by the Research Foundation of the Chang Gung Memorial Hospital, Taiwan (CMRPG8D1441), and has been registered in a publicly accessible registry (ClinicalTrials.gov number: NCT03128736). We enrolled 175 adult GERD subjects and randomized them in a 1:1 ratio into two sequence groups that defined the order in which they received single doses of dexlansoprazole (n = 88) and esomeprazole (n = 87) for an ITT. Written informed consent was obtained from each patient. The patients were asked to complete the Chinese GERDQ upon recruitment. Blood samples were collected to measure the fasting blood sugar, serum cholesterol, and triglyceride levels. In addition, the BMI was calculated. A complete medical history and demographic data were obtained from each patient. The primary end points were the complete symptom resolution (CSR) rates at days 1, 3, and 7. CSR was defined as no reflux symptoms sufficient to impair the quality of life before the end of the initial treatment phase. The main outcome measures were the CSR rates at days 1, 3, and 7 of the initial treatment period. All patients starting esomeprazole or dexlansoprazole as their initial treatment were included in the ITT analysis. Patients with poor drug compliance were excluded from the PP analysis.

**Research results**

Thirteen patients were lost during the follow up period, resulting in the inclusion of 81 patients in each group in the PP analysis. The CSRs for both groups were similar at days 1, 3, and 7. In the subgroup analysis, female patients achieved higher CSRs in the dexlansoprazole group than in the esomeprazole group at day 3 (38.3% vs 18.4%, P = 0.046). An increasing trend toward CSR was observed at day 7 (55.3% vs 36.8%, P = 0.09). In the esomeprazole group, female sex was a negative predictive factor for CSR at post-dose days 1 (OR = 1.249 ± 0.543; 95%CI: 0.287 (0.099-0.832), P = 0.022) and 3 (OR = -1.254 ± 0.519; 95%CI: 0.285 (0.103-0.789), P = 0.016). Patients with spicy food eating habits achieved lower CSRs on day 1 (37.3% vs 21.4%, OR = -0.569 ± 0.438; 95%CI: 0.380 (0.161-0.896), P = 0.027).

**Research conclusions**

The conclusion of this study was that the overall CSR rates for GERD were similar on days 1 through 7 for both the dexlansoprazole and esomeprazole groups, although a higher incidence was observed on day 3 in female patients who received a single dose of dexlansoprazole. The findings of this study are novel, since no report has investigated the short-term clinical effects of dexlansoprazole 60 mg vs esomeprazole 40 mg. This comparison represents an unmet need for GERD treatment in real-world clinical practice. The findings in this study could have important implications for clinical practice in the future for the treatment of grade A and B GERD patients. Furthermore, this study observed that female sex was a negative predictive factor for CSR at post-dose days 1 and 3 in the esomeprazole group. These findings implied that esomeprazole at 40 mg required more time (3 d) than dexlansoprazole at 60 mg to attain CSR in females. The new theories proposed suggest that these observations could be due to differences in the pharmacokinetics of esomeprazole and dexlansoprazole. Esomeprazole is time- and dose-dependent, especially at days 1 and 5. No accumulation of dexlansoprazole occurs after multiple once-daily doses at 60 mg. The authors validated this possibility by calculating the Cmax of dexlansoprazole, which was 16 μmol/L on day 1 and 17.67 μmol/L on day 5. As a result, dexlansoprazole almost achieved the target concentration on day 1. In addition, there is ample evidence that estrogen and progesterone enhance relaxation of the lower esophageal sphincters and induce GERD symptoms, especially in post-menopausal women taking hormone replacement therapy. These hypotheses could explain why female patients taking esomeprazole needed at least 3 more days to accumulate a sufficient plasma concentration to achieve plateau levels and desirable clinical effects.

**Research perspectives**

The important message of this study is that rapid onset PPIs for fast symptom relief remains an unmet need for GERD treatment. However, no report has investigated the short-term clinical effects of dexlansoprazole 60 mg vs esomeprazole 40 mg. Thus, the findings of this pilot study are novel and may have important implications for clinical practice in the future for the treatment of patients with grades A and B GERD. This pilot study was hampered by the small sample size. We believe that large-scale randomized controlled trials are necessary to further fulfill the future perspectives.

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