Turk J Gastroenterol *2016; 27: 408-14*

Comparison of the effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on intragastrıc pH in extensive metabolizer patients with gastroesophageal reflux disease

ESOPHAGUS

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Original Article

ABSTRACT

Background/Aims: Studies on the therapeutic efficacy of proton pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD) have been recently published. In most of these studies, comparison of only two PPIs have been made. There are few studies on the comparison of four or more PPIs. We aimed to compare the acid inhibitory effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on days 1 and 5 of treatment in patients with GERD, who were extensive metabolizers in regard to the CYP2C19 genotype.

Materials and Methods: *Helicobacter pylori*-negative with typical symptoms of GERD patients were randomly divided into four treatment groups. Efficacy analysis on days 1 and 5 were performed on the four groups which comprised 10 (esomeprazole), 11 (rabeprazole), 10 (lansoprazole), and 10 (pantoprazole) patients.

Results: On day 1 of PPI treatment, the mean percentage of time with intragastric pH>4 were 54%, 58%, 60%, and 35% for the groups, respectively, and on day 5, these values were 67%, 60%, 68%, and 59%, respectively. Esomeprazole, rabeprazole, and lansoprazole were found to be superior to pantoprazole on the first day of treatment.

Conclusion: Pantoprazole is a less potent proton pump inhibitor than the other PPIs tested on the first day of treatment. When the time needed to raise the intragatric pH to over 4 was evaluated, esomeprazole was found to have the most rapid action, followed by lansoprazole and rabeprazole.

Keywords: Extensive metabolizer, GERD, PPI, intragastric pH, CYP2C19

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common acid-related disorder. Typical symptoms of GERD are pirosis and regurgitation (1). The prevalence of GERD is increasing worldwide, especially in Western countries (2,3). The maintenance of intragastric pH above four is critical in the treatment of GERD. Proton pump inhibitors (PPIs) are the most effective drugs in the treatment of reflux esophagitis (4,5). One of the most common methods to demonstrate the acid inhibitory effect of PPIs is the 24-h intragastric pH measurement. Intragastric pH monitorization is a very sensitive method of measurement for the comparison of anti-secretory treatments (6). The parameters used in clinical trials for assessing the intragastric acid suppression efficiency of PPIs are the mean intragastric pH over 24 h and mean percentage of time with an intragastric pH>4 (7). The onset of action after the first dose is another reference parameter used in trials.

Cytochrome P450 2C19 (CYP2C19) genotypes and the existence of *Helicobacter pylori (H. pylori)* markedly influence the degree of the intragastric acid inhibitory effect of PPIs. As better acid suppression is seen in poor metabolizers of PPIs in regard to the CYP2C19 genotype, less acid supression is seen in extensive metabolizers (8). According to the polymorphism of CYP2C19, poor metabolizers in the West and Turkey account for

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Received: January 19, 2016 **Accepted:** June 28, 2016

approximately 1%–3% of the population, whereas this rate has been reported as approximately 20% in the far East (9,10). Optimally, the CYP2C19 genotype should be taken into consideration when comparing the effects of PPIs; however, most of the relevant studies have not provided data on this so far.

Some studies on the therapeutic efficacy of PPIs have been published recently. In these studies, the efficacy of different PPIs on intragastric pH have been compared (11-24). In most of these studies, a comparison of only two PPIs has been made and there are few studies comparing four or more PPIs (19-21). The results found in these studies are important in terms of their guidance for selecting PPIs.

In this study, we aimed to compare the effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on the percentage of time with an intragastric pH greater than 4 and on the 24-h mean pH on days 1 and 5 in Turkish patients with symptoms of GERD who were extensive metabolizers with the CYP2C19 genotype and *H. pylori* negative.

MATERIALS AND METHODS

Our study is a single-center, randomized, prospective study with four arms and was performed between February 2008 and January 2009 in Kocaeli University Hospital. The study was conducted in accordance with the Helsinki Declaration principles, after first getting approval from the ethics comittee of Kocaeli University (Registration number: 2007/119, January 08, 2008).

H. pylori-negative patients over 18 years old with pyrosis and/or regurgitation occurring once a week or more and ongoing for more than 6 months and who were admitted to Kocaeli University Gastroenterology Outpatient Clinic were enrolled in the study. All the patients underwent upper gastrointestinal endoscopy before study entry. Exclusion criteria were gastric outlet obstruction, patients with more than a 2-cm hiatal hernia detected by endoscopy, active peptic ulcer, upper gastrointestinal cancer, a history of upper gastrointestinal surgery, patients with motility disorders like Systemic Sclerosis and Achalasia, pregnancy or lactation and histological evidence of atrophic gastritis, and alarm symptoms of upper GI malignancies (e.g., hematemesis, dysphagia, odinophagia, melena). The 13C-urea breath and histology test were performed for the diagnosis of *H. pylori* infection. Other exclusion criteria were a significant comorbid disease and the use of any medication. Previously, reflux patients with refractory conditions to PPIs were excluded from the study. Afterwards, written consent was taken from all the patients who agreed to participate in the study. A full medical history was taken and a physical examination performed at enrollment.

A CYP2C19 mutation analysis study was performed in all patients enrolled in the study. Genetic mutation analysis was performed by using the LigtMix CYP2C19*2 and CYP2C19*3 genomic kits. Patients with the wild-type CYP2C19 genotype were enrolled in the study. Patients in whom heterozygous or homozygous mutation was detected were excluded.

Proton pump inhibitors, histamin 2 receptor antagonists (H2RA), prokinetics, and antispasmodics were not permitted in the 14 days prior to the start of the study. For symptom control, the use of anti-acids were permitted until the last day before the study.

Eligible patients were randomized into four study groups to receive once-daily oral treatment with esomeprazole 40 mg (enteric coated tablet), rabeprazole 20 mg (enteric coated tablet), lansoprazole 30 mg (micropellet capsule), or pantoprazole 40 mg (enteric coated tablet). The drug doses used in our study are the standard doses ued in Turkey.

The esophageal manometry measurements of the patients in the study were normal. After manometric localization of the lower esophageal sphincter, 48-h pH-meter measurements were performed in all patients. The calibration of the catheter was made using standard buffers at pH 7.00 and 4.00 before and after the pH recording. Following an overnight fasting, a pH-meter catheter was inserted intranasally after determining the location of the lower esophageal sphincter by manometry. A proximal electrode was also placed 5 cm above the lower esophageal sphincter. while a distal electrode was located 10 cm below the lower esophageal sphincter to measure the intragastric pH. The equipment used in the studies was a MMS Orion pH-data logger (Version 8.3s, Medical Measurement System; the Netherlands). In the first 24-h period of the 48-h pH-meter measurement, no medication was given to the patients. After the first day, the patients took PPI 30 min before a standardized breakfast at 9.00 am on day 2. After the 48-h measurement, the pH-meter catheters were removed at 9.00 am before the second dose of PPI. Patients were advised to take their PPIs orally as a single dose regularly every morning at 9.00 am, 30 min before breakfast. On the fifth day of treatment, another 24-h pH-meter measurement was performed using the same protocol at 9.00 am following an overnight fast. The catheter was placed at the same level on day 5 of the patients pH monitoring. After the 24-h measurement of the fifth day under PPI treatment, the procedure was ended on the sixth day at 9.00 am. All meals were standardized during the study days. Patients were advised not to drink alcohol, acidic or alkaline (cola beverages, mineral water) beverages, and to have breakfast, lunch, and dinner at 9.30 am, 1.00 pm, and 7.00 pm, respectively, during the study period. Treatment compliance was checked by counting the pills at the fifth day of the treatment. Rescue antacids were used except during pH metry recording. All the side effects were recorded throughout the study. The study design is shown in Figure 1.

All the pH traces were evaluated by a single gastroenterologist who was blinded to the study groups. The percentage of time

with an intragastric pH greater than 4 and the 24-h intragastric pH were analyzed during the 24-h period on the pretreatment day, the first day, and the fifth day. Patients whose on pretreatment day mean intragastric pH over 24 h was more than pH 2 were excluded from the study in order to avoid a bias between the groups, since the efficacy of the PPIs is better in patients with low acid secretion. Hourly (0–1, 1–2, 2–3, ...) mean pH values were measured over the 6 h after the first dose of treatment. These analyses were made with the MMS Database program mentioned above. The qualitative clinical response was not assessed because the number of patients was small.

Statistical analysis

For statistical analysis, continuous variables were expressed as the mean±standard deviation (SD), and categorical data were expressed as numbers or percentages. The means and standard deviations of the demographical variables of the groups (age, BMI) and pH-meter parameters (median and ranges of intragastric pH over 24 h, median and ranges of percentage of time with an intragastric pH>4, mean and standard deviation of hourly pH after the first dose) were calculated. Normally distributed data were analyzed as the mean and SD, while abnormally distributed data were analyzed as the median and ranges. The categorical variables (e.g., sex) were compared using Chi-squared statistics. For statistical analysis between groups, the Kruskall–Wallis H test was used, while for the dual comparison of groups on statistically significant parameters, the Mann–Whitney U test was used and $p<0.05$ was considered to be significant. SPSS 11.0 software (SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis. In this study, the number of patients required for 80% power and 5% type 1 error was calculated to be at least 42 (25).

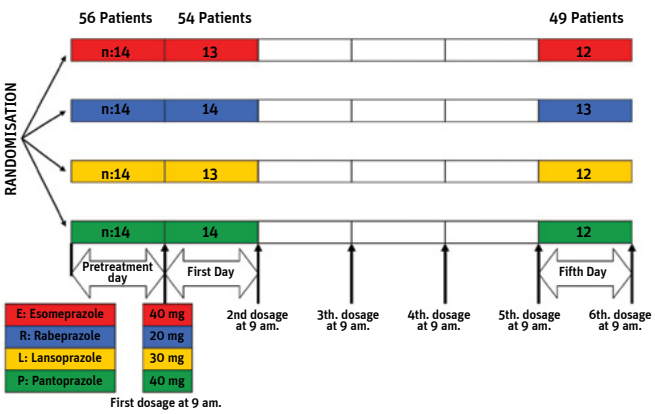

Figure 1. Study design (Color Rectangles: Intragastric pH Monitorization days)

RESULTS

Fifty-six patients were randomized into four groups, all of which included 14 patients. Seven patients were excluded from the efficacy analyses because of technical deficiencies in our study. Two patients were excluded from the study for not completing the 48-h pH recording, and four patients for not returning to the fifth day pH recording, and one patient for not adhering to the medication time. In the pretreatment 24-h pH-meter recordings of the remaining 49 patients, the mean percentage of time with an intragastric pH>4 was found to be 8.8±7.7%. To avoid causing a bias between the groups, eight patients whose median intragastric pH over 24 h was more than pH 2 were excluded from the study. There were no side effects detected related to the medical therapy. Therefore, the efficacy analysis on day 1 and day 5 included 10 (esomeprazole), 11 (rabeprazole), 10 (lansoprazole), and 10 (pantoprazole) patients.

The baseline demographic characteristics of the study patients are presented in Table 1. Sex, age, and body mass index (BMI) were not statistically significantly different between the groups. The ages of the patients ranged from 28 to 45 years. Fourteen of the patients had mild erosive esophagitis, but erosive esophagitis was not statistically significantly different between the groups.

In the pretreatment 24-h pH-meter measurements, the median (ranges) percentages of time with an intragastric pH>4 were 2.4% (0.3–14.3), 7.4% (0.9–11.3), 2.8% (0.4–15.5), and 6.4% (0.7–14.9) for the esomeprazole, rabeprazole, lansoprazole, and pantoprazole groups, respectively, and there was no statistically significant difference between the groups. On day 1 of PPI treatment, the median (ranges) percentages of time with an intragastric pH>4 were 56% (21–87), 58% (31–83), 57% (33–91), and 27% (5–77) for the groups, respec-

Table 1. Baseline demographic characteristics of the four group

Characteristics	Esomeprazole 40 mg	Rabeprazole 20 mg	Lansoprazole 30 mg	Pantoprazole 40 mg	P
Number of patients	10	11	10	10	NS
Sex (male/female)	4/6	5/6	4/6	4/6	NS
Mean age (years)±SD	41.9±12.9	44.4±6.4	41.6±9.3	38.9±11.3	NS
Mean BMI (kg/m^2)±SD	26.8±5.6	26.1±3.0	26.6±3.5	28.2±5.6	NS
Esophagitis LA-A	3	2	3	2	NS
Esophagitis LA-B	1	2	0	1	NS

SD: standard deviation; BMI: body mass ındex; LA-A: Los Angeles Classification; NS: not significant

tively, while on day 5 these values were 68% (36–90), 63% (22–82), 65% (35–99), and 61% (35–98), respectively. On day 1, there was no statistically significant difference among the esomeprazole, rabeprazole, and lansoprazole groups in regard to the median percentage of time with an intragastric pH>4, but the esomeprazole, rabeprazole, and lansoprazole groups had a statistically significant superior acid suppressive effect compared to the pantoprazole group ($p<0.05$). However, on day 5 of treatment, there was no statistically significant difference between the groups in regard to the median percentage of time with an intragastric pH>4. The pretreatment, day 1, and day 5 median (ranges) percentages of time with an intragastric pH>4 of the four groups are displayed in Figure 2.

The median 24-h pH was 1.2 for the esomeprazole and lansoprazole groups and 1.1 for the rabeprazole and pantoprazole groups on the pretreatment day. The median 24-h intragastric pH on treatment day 1 was 4.2 (1.4–5.9), 4.4 (2.0–5.1), 4.1 (2.7–5.2), and 2.1 (1.0–6.0) for the esomeprazole, rabeprazole, lansoprazole, and pantoprazole groups, respectively, while on day 5, these values were 4.5 (2.5–6.2), 4.6 (2.2–5.5), 4.4 (2.8–6.0), and 4.4 (2.3–5.6), respectively. The pretreatment and day 5 median 24-h intragastric pH values did not differ between the groups in terms of statistical significance; however, values for the esomeprazole, rabeprazole, and lansoprazole groups were statistically superior to the pantoprazole group ($p<0.05$) on day 1. The pretreatment, day 1, and day 5 median (ranges) 24-h pH values are displayed in Figure 3.

The time needed to raise the intragastric pH over 4 after the first dose of drug was 3 h, 4 h, and 6 h for the esomeprazole, lansoprazole, and rabeprazole groups, respectively. However in the pantoprazole group, the mean pH value reached 3 in the second hour but then did not change until the sixth hour. The mean pH at the third hour after the first dose was 4.0±0.5, 2.6±0.6, 3.0±0.5, and 2.9±0.7, while the mean pH at fourth hour after the first dose was 4.1±0.6, 3.2±0.5, 4.0±0.5, and 2.9±0.6, and the mean pH at the sixth hour after the first dose was 4.8±0.6, 4.0±0.5, 4.3±0.7, and 3.2±0.7 for the esomeprazole, rabeprazole, lansoprazole, and pantoprazole groups, respectively. Esomeprazole was statistically superior to rabeprazole, lansoprazole, and pantoprazole ($p<0.05$) at the third hour after the first dose. Esomeprazole and lansoprazole were statistically superior to pantoprazole ($p<0.05$) at the fourth hour after the first dose. Esomeprazole was statistically superior to pantoprazole ($p<0.05$) at the sixth hour after the first dose. Considering the time needed to raise the pH over 4 after the first dose, the most rapid action was observed for esomeprazole, followed in order of increasing time by lansoprazole, rabeprazole, and pantoprazole, respectively. The hourly mean pH changes achieved by the four drugs after the first dose are displayed in Figure 4.

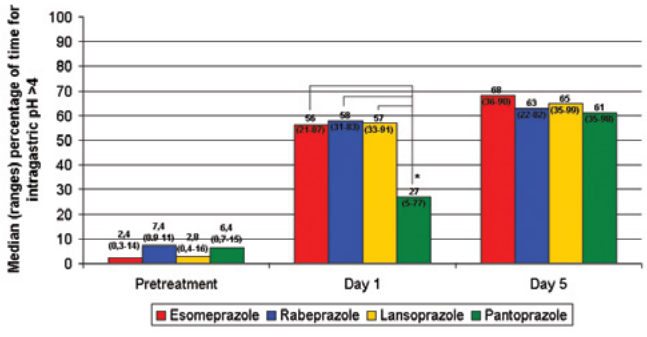

Figure 2. Median (ranges) percentage of time with an intragastric pH>4 on the pretreatment, first, and fifth days of treatment of once-daily oral treatment with esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg.
*Pantoprazole vs. esomeprazole, rabeprazole, and lansoprazole on day 1 ($p<0.05$).

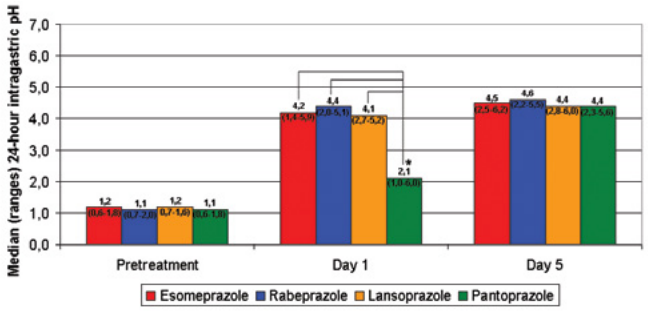

Figure 3. Median (ranges) 24-h intragastric pH values for pretreatment, first, and fifth treatment days of once-daily oral treatment with esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg.
*Pantoprazole vs. esomeprazole, rabeprazole, and lansoprazole on day 1 ($p<0.05$).

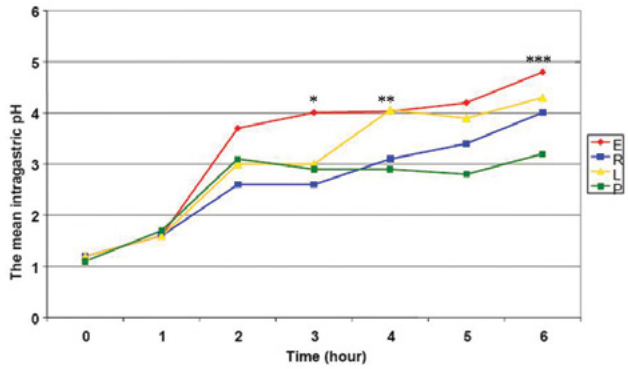

Figure 4. Hourly mean pH values provided after the first doses of once-daily oral treatment with esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg.
(E: esomeprazole; R: rabeprazole; L: lansoprazole; P: pantoprazole)
*Esomeprazole was statistically superior to rabeprazole, lansoprazole, and pantoprazole at the third hour after the first dose ($p<0.05$).
**Esomeprazole and lansoprazole were statistically superior to pantoprazole at the fourth hour after the first dose ($p<0.05$).
***Esomeprazole was statistically superior to pantoprazole at the sixth hour after the first dose ($p<0.05$).

Original Article

DISCUSSION

In the present study, we conducted the examinations using four different PPIs in *H. pylori*-negative gastroesophageal reflux patients who were extensive metabolizers, and we found the median percentages of time with an intragastric pH>4 on the first day of treament were 56%, 58%, 57%, and 27% for esomeprazole, rabeprazole, lansoprazole, and pantoprazole, respectively. The esomeprazole, rabeprazole, and lansoprazole groups were found to exhibit statistically significant superiority to the pantoprazole group on the first day of treatment. Moreover, the median 24-h intragastric pH values on the first treatment day were found to be similar in the esomeprazole (4.2), rabeprazole (4.4), and lansoprazole (4.1) groups but lower in the pantoprazole group (2.1). Therefore esomeprazole, rabeprazole, and lansoprazole were statistically superior for acid suppression compared to pantoprazole on the first day of treatment. However, there was no statictically significant difference between the groups in regard to the median percentage of time with an intragastric pH>4 and the median intragastric pH on the fifth treatment day.

In a randomized, crossover Swedish study conducted by Röhss et al. (19), four treatment groups were established in which esomeprazole was compared with one of the other PPIs in each arm: esomeprazole 40 mg was compared with lansoprazole 30 mg in the first arm, with omeprazole 20 mg in the second arm, with pantoprazole 40 mg in the third arm, and with rabeprazole 20 mg in the fourth arm. In all the groups, esomeprazole was found to be superior to all the other PPIs in regard to the mean percentage of time with pH>4 both on the first day and on the fifth day of treatment. Our study revealed a higher median percentage of time with pH>4 and the first day median 24-h pH compared to the study of Röhss et al. (19). We found no statistically significant difference between the esomeprazole, lansoprazole, and rabeprazole groups in regard to the first day median percentage of time with an intragastric pH>4 and the median intragastric pH values. However, all these three PPIs showed statistically significant superiority over pantoprazole in terms of their acid suppressive effect. The fifth day results of the lansoprazole, rabeprazole, and pantoprazole groups were lower in the study mentioned above compared to our study.

In a double-blind, randomized, crossover study conducted by Pantoflickova et al. (20), the efficacies of rabeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, and omeprazole 20 mg/day on the first day were compared. Here, rabeprazole showed a statistically significant superiority to the other PPIs in regard to both the mean percentage of time with an intragastric pH>4 and the intragastric median pH. When the results of rabeprazole, lansoprazole, and pantoprazole in this study were considered, we noticed that the first day median percentage of time with an intragastric pH>4 and the median 24-h intragastric pH values achieved with these drugs (especially with rabeprazole and lansoprazole) were higher in our study.

In a crossover, five arm study conducted by Miner et al. (21) in *H. pylori*-negative patients with GERD, the efficacy of esomeprazole 40 mg/day, rabeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, and omeprazole 20 mg/day on the fifth treatment day were compared and the mean percentage of time with an intragastric pH>4 achieved by esomeprazole was found to be higher than the other PPIs in terms of statistical significance. In this study, esomeprazole was statistically superior to lansoprazole, pantoprazole, and omeprazole in regard to the fifth day mean intragastric pH values. The mean age (44±11) and percentage of time with an intragastric pH>4 in their study are similar to the results of our study. However, in our study, there was no statistically significant difference between the groups on the fifth day.

In our study, the time needed to raise the intragastric pH over 4 after the first dose, which is the critical value in GERD treatment, was found to be 3 h for the esomeprazole group, 4 h for the lansoprazole group, and 6 h for the rabeprazole group. As for the pantoprazole group, it was seen that the mean pH reached the value of 3 in the second hour and then did not change until the sixth hour. In the above-mentioned study conducted by Pantoflickova et al. (20), when the time needed to raise the intragastric Ph>4 after the first doses of rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and omeprazole20 mg was considered, the onset of action was the most rapid for lansoprazole, followed in order by omeprazole, rabeprazole, and pantoprazole. Esomeprazole, with the most rapid action in our study, was not included in that study. However, our results for lansoprazole, rabeprazole, and pantoprazole are similar to their results.

In an *in vitro* study conducted by Robinson and Horn (26), the inhibition rates of gastric H/K adenosine triphospahtase with rabeprazole, omeprazole, lansoprazole, and pantoprazole were studied, and it was reported that the *in vitro* inhibition of 80% of H/K ATP'ase enzyme was 5 min for rabeprazole and 15 min for omeprazole and lansoprazole, while pantoprazole could inhibit only 50% of the enzyme at the end of 45 min. The results of this *in vitro* study are comparable with the finding of late onset action of pantoprazole found in our study. Two factors may be effective in the late onset action of pantoprazole: first, the pKa1 and pKa2 values of pantoprazole are lower than the others, and second, pantoprazole is metabolized mainly by CYP2C19 unlike the others.

The above-mentioned studies were designed in crossover fashion, but CYP2C19 polymorphism, which markedly affects PPI metabolism, was not taken into consideration. To date, studies have shown that extensive, intermediate, and poor metabolizers of CYP2C19 affect the metabolism of individual PPIs at different rates. In a study conducted by Hunfeld et al. (27), the acid inhibitory effect and kinetics of pantoprazole were shown to be more influenced by the CYP2C19 genotype than that of esomeprazole. In another study by the same group (23),

esomeprazole 40 mg was shown to provide a more effective and faster acid inhibitory effect than rabeprazole 20 mg. In a study recently published by Sugimoto et al. (24), the acid inhibitory effects of rabeprazole were shown to be less influenced by the CYP2C19 genotype than by lansoprazole and omeprazole.

In our study, in contrast to other studies, lansoprazole was found to be as potent as esomeprazole and rabeprazole on the first day, while esomeprazole and lansoprazole were found to be more rapid than rabeprazole in regard to the onset of action after the first dose. In addition, the PPIs in our study achieved a higher median percentage of time with an intragastric pH>4 compared to the other studies. The potential factors for this difference might be due to a range of reasons, such as the higher mean age values (40 vs 30), resulting in decreased drug metabolism, the difference in standardized diet regimen and pH measurement technique, absorption changes due to drug formulation, the selection of a different patient population, or cytochrome p450 polymorphism resulting from the genetic differences of the study populations. As CYP2C19 polymorphism directly affects PPI metabolism, it would be reasonable to investigate the CYP polymorphism of other countries and to assess the literature data accordingly.

The strengths of our study were the determination of the extensive metabolizers of CYP2C19 polymorphism and our method of including only them, as well as İncluding in our study, four different PPIs in an independent study not funded by the pharmaceutical industry.

The limitations of our study include that this study was not designed as a crossover study. However, in our study to prevent intergroup bias, *H. pylori*-negative patients who had the extensive metabolizing genotype, which is encountered frequently in the caucasian race and in Turkey, were randomly enrolled in four groups. Moreover by performing pretreatment 24-h pH monitorization for every patient enrolled in the study, patients who on pretreatment day had a median intragastric pH over 24 h of more than pH 2 were excluded from the study as their pretreatment acid secretion was too low for inclusion. In our study, a pH-meter was used instead of multichannel intraluminal impedance pH. The aim of this study was to determine the intragastric acid inhibitory effect of PPIs. Therefore a pH-meter was sufficient for this aim.

As a conclusion, the present study demonstrates that pantoprazole is a less potent proton pump inhibitor than esomeprazole, lansoprazole, and rabeprazole on the first day of treatment in Turkish patients with symptoms of GERD who are extensive metabolizers with the CYP2C19 genotype and *H. pylori* negative. This difference disappears on the fifth day of treatment. As the time needed to raise the intragatric pH to over 4 after the first dose was evaluated, esomeprazole was found to have the most rapid action, followed by lansoprazole and rabeprazole. Our results may be important in the selection of on-demand PPI therapy in the treatment of GERD. PPIs that are used as on-demand therapy should be long and fast-acting. Our results suggest that esomeprazole, rabeprazole, and lansoprazole but not pantoprazole may be potential candidates for on-demand treatment in patients with extensive metabolizers.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.Ç., D.A.; Design - A.Ç., D.A.; Supervision - S.H.; Materials - D.A., B.T.K.; Data Collection and/or Processing - D.A., B.T.K.; Analysis and/or Processing - A.Ç.; Literature Review - A.Ç., D.A., O.K., Ö.Ş.; Writer - A.Ç., D.A.; Critical Review - A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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