CLINICAL TRIALS

Acid-suppressive effects of rabeprazole, omeprazole, and lansoprazole at reduced and standard doses: A crossover comparative study in homozygous extensive metabolizers of cytochrome P450 2C19

Background and Objectives: **To improve clinical outcomes of the initial therapy for gastroesophageal reflux disease, intragastric pH should be above 4.0 for more than 20 hours a day (83.3%) and nocturnal gastric acid breakthrough, defined as 60 continuous minutes of intragastric pH below 4.0 at night, should be inhibited. A "step-down" therapy sometimes fails because of insufficient acid suppression. Therefore we compared the acid-suppressive effects of proton pump inhibitors.**

Methods: **This was a prospective, randomized, open-label, 8-way crossover study. In 9 healthy *Helicobacter pylori*–negative cytochrome P450 (CYP) 2C19 homozygous extensive metabolizers, intragastric pH was measured for 24 hours on day 7 of treatment with rabeprazole, omeprazole, and lansoprazole orally administered once daily at reduced and standard doses.**

Results: **Compared with baseline data (7% [range, 5%-20%]), the median values of the 24-hour percent of time that intragastric pH was above 4.0 significantly increased but did not exceed 83.3% under any of the 7 regimens, which were as follows: 10 mg rabeprazole (51% [range, 28%-78%], $P < .01$), 20 mg rabeprazole (59% [range, 36%-83%], $P < .01$), 10 mg omeprazole (26% [range, 4%-33%], $P < .05$), 20 mg omeprazole (48% [range, 31%-73%], $P < .01$), 40 mg omeprazole (62% [range, 47%-87%], $P < .01$), 15 mg lansoprazole (34% [range, 5%-51%], $P < .05$), and 30 mg lansoprazole (56% [range, 20%-76%], $P < .05$). Significant differences were observed among 10, 20, and 40 mg omeprazole (10 mg versus 20 mg, $P < .01$; 10 mg versus 40 mg, $P < .01$; and 20 mg versus 40 mg, $P < .05$) and between 15 and 30 mg lansoprazole ($P < .01$), whereas no significant difference was observed between 10 and 20 mg rabeprazole. Nocturnal gastric acid breakthrough was observed under all regimens.**

Conclusions: **Rabeprazole, omeprazole, and lansoprazole, given once daily at standard doses, cannot be expected to achieve ideal acid suppression for the initial therapy for gastroesophageal reflux disease in *Helicobacter*–negative CYP2C19 homozygous extensive metabolizers. Rabeprazole 10 mg may be appropriate for step-down therapy. (Clin Pharmacol Ther 2006;79:144–52.)**

Tomohiko Shimatani, MD, PhD, Masaki Inoue, MD, PhD, Tomoko Kuroiwa, MS, Jing Xu, MD, Hiroshi Mieno, MD, PhD, Masuo Nakamura, MD, and Susumu Tazuma, MD, PhD *Hiroshima and Tokyo, Japan*

From the Department of General Medicine, Hiroshima University Hospital, Department of Geriatric Health Sciences, Graduate School of Health Sciences, Hiroshima University, and Department of Gastroenterology, Hiroshima Railway Hospital, Hiroshima, and Department of Internal Medicine, Wakasagi Medical Clinic, Tokyo.

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Reprint requests: Tomohiko Shimatani, MD, PhD, Department of General Medicine, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail: *tshima@hiroshima-u.ac.jp*

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Proton pump inhibitors (PPIs), such as omeprazole, lansoprazole, and rabeprazole, are first-line drugs for treatment of gastroesophageal reflux disease (GERD). In most patients PPIs at standard doses can control GERD within 8 weeks; however, approximately 10% to 20% of GERD patients have refractory symptoms because of insufficient acid suppression despite administration of PPIs.[1] In addition, PPIs at reduced doses are often administered as maintenance therapy for GERD[2-11] and provide superior cure rates to histamine H_2 receptor antagonists (H_2-RAs).[8-11] However, few studies have demonstrated to what degree each PPI at standard or reduced doses inhibits acid secretion.

The acid-suppressive effects of PPIs are affected by certain factors. PPIs are mainly metabolized by the 2C19 and 3A4 isoforms of the hepatic cytochrome P450 (CYP) mixed-function oxidase system (ie, CYP2C19 and CYP3A4),[12] and recent studies have revealed that CYP2C19 has 3 hereditary genotypes: homozygous extensive metabolizers, with higher enzymatic activity; heterozygous extensive metabolizers, with moderate enzymatic activity; and poor metabolizers, with markedly impaired enzyme activity.[13-16] Therefore, in CYP2C19 homozygous extensive metabolizers, the acid-suppressive effects of omeprazole and lansoprazole are reduced compared with heterozygous and poor metabolizers.[17-22] These interindividual differences are reflected in clinical outcomes: CYP2C19 genotype status affects the cure rate in GERD patients treated with 30 mg lansoprazole once daily for 8 weeks,[23,24] and the cure rate in CYP2C19 homozygous extensive metabolizer patients with high-grade GERD (ie, grades C and D according to the Los Angeles classification) was extremely low (16.7%).[23] Furthermore, the acid-suppressive effects of PPIs are also affected by *Helicobacter pylori* status; in *H pylori*–negative subjects the acid-suppressive effects are generally reduced compared with those in *H pylori*–positive subjects.[25,26] Therefore it is important for the acid-suppressive effects of each PPI to be reassessed in relation to CYP2C19 genotype and *H pylori* status.

Rabeprazole, a second-generation PPI, causes potent and long-lasting inhibition of acid secretion.[27-29] Unlike omeprazole and lansoprazole, rabeprazole is metabolized mainly via a nonenzymatic pathway, with minor CYP2C19 and CYP3A4 involvement.[16,30] Therefore the acid-suppressive effect of rabeprazole is considered to be less affected by CYP2C19 genotype status.[18,19,22]

Individual PPIs differ with respect to the onset, duration, and potency of their acid-suppressive effects as measured by several parameters. Maximum plasma concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) are linearly related to the PPI dose, whereas the time to C_{max} (t_{max}) and elimination half-life ($t_{½}$) are dose-independent.[30-32] A significant correlation exists between the AUC of a PPI and its degree of acid-suppressive effect.[32-34] This pharmacokinetic/pharmacodynamic relationship appears to be described by the maximum effect (E_{max}) model, with an upper AUC limit above which no further increase in intragastric pH can be expected.[35,36] Plasma PPI levels are related to CYP2C19 genotype status, and this can predict the degree of acid-suppressive effect.[17,19,23] However, these results suggest that these parameters are not useful for comparing acid-suppressive effects among PPIs; therefore intragastric pH needs to be measured.

Therefore we measured intragastric pH during administration of different dose regimens of 3 PPIs currently available in Japan—rabeprazole, omeprazole, and lansoprazole—in *H pylori*–negative CYP2C19 homozygous extensive metabolizers. In particular, we sought to compare the acid-suppressive effects of reduced and standard doses of each PPI, as well as to assess the regimens that achieved sufficient acid-suppression for initial and maintenance therapies for GERD. To our knowledge, this is the first report of a crossover-designed comparative pharmacodynamic study comparing 3 PPIs at reduced and standard doses.

In this comparative study we considered that *H pylori*–negative CYP2C19 homozygous extensive metabolizers were the most appropriate subjects, because they comprise 56.7% to 81.0% of the European and North American populations and 27.7% to 38.2% of the Asian population[37-44] and most GERD patients are *H pylori*–negative.[45,46]

METHODS

Subjects. Nine healthy male Japanese *H pylori*–negative CYP2C19 homozygous extensive metabolizers participated in this study. The subjects, aged between 21 and 30 years (median, 23 years) and weighing 57 to 85 kg (median, 64 kg), had no history of gastrointestinal or hepatobiliary diseases or of eradication therapy for *H pylori* and took no regular medications. The full medical history of each subject was recorded, and each underwent a physical examination.

H pylori infection. *H pylori* infection was determined by measuring the serum titer of immunoglobulin G antibodies to *H pylori* by an enzyme immunoassay (HM-CAP Kit; Enteric Products, Stony Brook, NY) and by the carbon 13–urea breath test. Only individuals

with negative results for both tests were considered to be free from *H pylori* infection.

CYP2C19 genotyping. Genotyping procedures identifying the *CYP2C19* wild-type (**1*) gene and the 2 mutated alleles, *CYP2C19*2* in exon 5 and *CYP2C19*3* in exon 4, were performed by a polymerase chain reaction–restriction fragment length polymorphism method, originally described by de Morais et al,[47,48] with minor modifications as reported by Kubota et al,[15] at the laboratory center at SRL, Tokyo, Japan. The subjects were determined to be homozygous extensive metabolizers by the absence of *CYP2C19*2* in exon 5 and *CYP2C19*3* in exon 4 (ie, **1/*1*).

Twenty-four–hour intragastric pH monitoring. Before each recording session, a glass electrode (CM-181; Chemical Instrument, Tokyo, Japan) was calibrated in buffer solutions at pH 6.86 and 4.01. At 4 PM, the pH electrode was inserted through the nose and the tip was fluoroscopically positioned in the upper portion of the gastric corpus (10 cm below the gastroesophageal junction) and connected to a portable digital recorder (CR-5501 or PH-101Z; Chemical Instrument). At 5 PM, measurement of the intragastric pH was started and continued for 24 hours. At fixed times (dinner at 6 PM, breakfast at 8 AM, and lunch at noon), standardized meals were consumed (total calories, 8000 kJ/d [protein, 70 g; lipids, 50 g; and carbohydrate, 290 g]). Subjects were free to drink water during the 24-hour period but were not allowed to smoke, although other normal daily activities were not restricted.

Study protocol. This was a prospective, randomized, open-label, 8-way crossover study. In a randomized order, each subject received either 10 mg or 20 mg rabeprazole; 10 mg, 20 mg, or 40 mg omeprazole; 15 mg or 30 mg lansoprazole; or placebo orally once daily after breakfast for 7 consecutive days. Intragastric pH was measured 8 times, on the last day of each of the 8 periods of drug or placebo administration. Between each period of administration, there was a washout period of 2 weeks or more.

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guideline on Human Genome and Genetic Analyses in Japan and was approved by the Ethical Committee of Hiroshima University Hospital, Hiroshima, Japan. Written informed consent was obtained from all subjects before the entry study.

Data analysis. After the 24-hour monitoring of intragastric pH, the recorded values were transferred to a personal computer for processing and analysis by use of a commercially available software program (Chemical Instrument). The median value of intragastric pH and the percent of time that intragastric pH was above 4.0, which are widely used and represent the degree of gastric acid suppression, were calculated.

Nocturnal gastric acid breakthrough was defined as at least 60 continuous minutes of intragastric pH below 4.0 during the nighttime period (10 PM to 6 AM).[49]

Statistical analysis. The parameters were expressed as median values (ranges). Differences in these parameters among each regimen were determined by the Wilcoxon signed rank test. Statistical analysis was performed with SAS software (SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant.

RESULTS

There were no adverse events during the study, which was completed according to the protocol by all 9 subjects.

Intragastric pH profiles. The 24-hour intragastric pH (median pH per hour) profiles without medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole once daily after breakfast are shown in Fig 1. In the daytime period (6 AM to 10 PM), intragastric pH values increased above 4.0 for long periods with 10 mg and 20 mg rabeprazole, 20 mg and 40 mg omeprazole, and 30 mg lansoprazole, as compared with those values without medication.

With 10 mg omeprazole and 15 mg lansoprazole, intragastric pH values hardly increased above 4.0 throughout the 24-hour period.

Median values of intragastric pH. Box-whisker plots of the median values of intragastric pH during the 24-hour and nighttime periods without medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole once daily after breakfast are shown in Fig 2 and Table I. Compared with the baseline data, the median values of 24-hour intragastric pH increased significantly with all 7 regimens: 10 mg rabeprazole ($P < .01$), 20 mg rabeprazole ($P < .01$), 10 mg omeprazole ($P < .05$), 20 mg omeprazole ($P < .01$), 40 mg omeprazole ($P < .01$), 15 mg lansoprazole ($P < .01$), and 30 mg lansoprazole ($P < .01$). The values in the nighttime period also significantly increased in 6 of 7 regimens: 10 mg rabeprazole ($P < .01$), 20 mg rabeprazole ($P < .01$), 20 mg omeprazole ($P < .01$), 40 mg omeprazole ($P < .01$), 15 mg lansoprazole ($P < .05$), and 30 mg lansoprazole ($P < .01$). The regimen of 10 mg omeprazole did not increase nighttime values significantly.

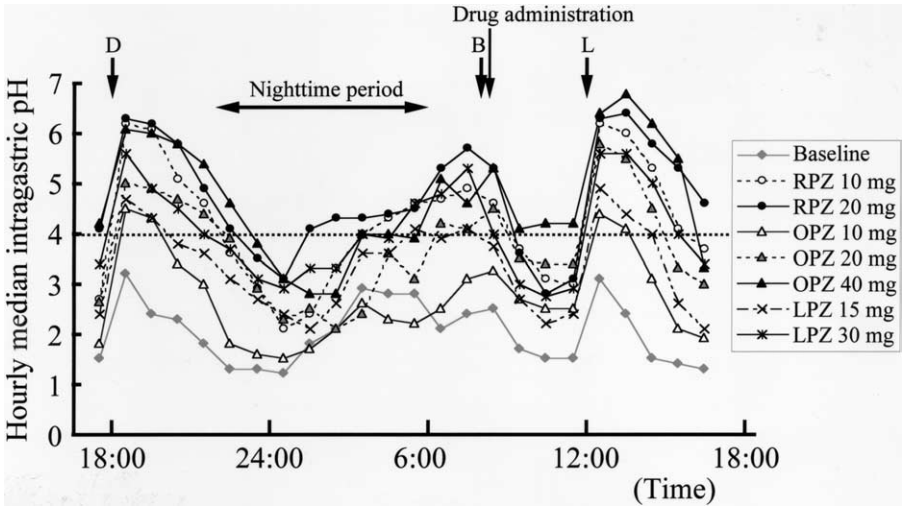

Fig 1. Profiles of 24-hour intragastric pH (median pH per hour) without any medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole administered orally once daily after breakfast in *Helicobacter pylori*–negative CYP2C19 homozygous extensive metabolizers. RPZ, Rabeprazole; OPZ, omeprazole; LPZ, lansoprazole; D, dinner; B, breakfast; L, lunch.

With 10 mg, 20 mg, and 40 mg omeprazole ($P < .01$ for 10 mg versus 20 mg, $P < .01$ for 10 mg versus 40 mg, and $P < .01$ for 20 mg versus 40 mg during the 24-hour period and $P < .01$ for 10 mg versus 20 mg and $P < .05$ for 10 mg versus 40 mg during the nighttime period) and 15 mg and 30 mg lansoprazole ($P < .05$ during the 24-hour and nighttime periods), the median values of intragastric pH in each time period increased significantly in a dose-dependent manner; however, no significant difference was observed between 10 mg and 20 mg rabeprazole.

Percent of time that intragastric pH was above 4.0. Box-whisker plots of the percent of time that intragastric pH was above 4.0 during the 24-hour and nighttime periods without medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole once daily after breakfast are shown in Fig 3 and Table I. Compared with the baseline data, the percent of time that intragastric pH was above 4.0 during a 24-hour period increased significantly with all 7 regimens: 10 mg rabeprazole ($P < .01$), 20 mg rabeprazole ($P < .01$), 10 mg omeprazole ($P < .05$), 20 mg omeprazole ($P < .01$), 40 mg omeprazole ($P < .01$), 15 mg lansoprazole ($P < .05$), and 30 mg lansoprazole ($P < .05$). These parameters increased significantly during the nighttime period with 6 of 7 regimens: 10 mg rabeprazole ($P < .01$), 20 mg rabeprazole ($P < .01$), 20 mg omeprazole ($P < .01$), 40 mg omeprazole ($P < .01$), 15 mg lansoprazole ($P < .05$), and 30 mg lansoprazole ($P < .01$).

With 10 mg, 20 mg, and 40 mg omeprazole ($P < .01$ for 10 mg versus 20 mg, $P < .01$ for 10 mg versus 40 mg, and $P < .05$ for 20 mg versus 40 mg) and 15 mg and 30 mg lansoprazole ($P < .01$), the percent of time that intragastric pH was above 4.0 during the 24-hour period increased significantly in a dose-dependent manner; however, no significant difference was observed between 10 mg and 20 mg rabeprazole.

Incidence of nocturnal gastric acid breakthrough. In 6 of 7 regimens, all 9 subjects had nocturnal gastric acid breakthrough. With 20 mg rabeprazole, this occurred in 8 of 9 subjects.

DISCUSSION

In this study, in *H pylori*–negative CYP2C19 homozygous extensive metabolizers, the acid-suppressive effect of a reduced dose of rabeprazole, 10 mg, was comparable to those of standard doses of rabeprazole, 20 mg, as well as omeprazole, 20 mg and 40 mg, and lansoprazole, 30 mg. Significant differences were observed in acid-suppressive effects among 10 mg, 20 mg, and 40 mg omeprazole, as well as between 15 mg and 30 mg lansoprazole, whereas no significant difference was observed between 10 mg and 20 mg rabeprazole.

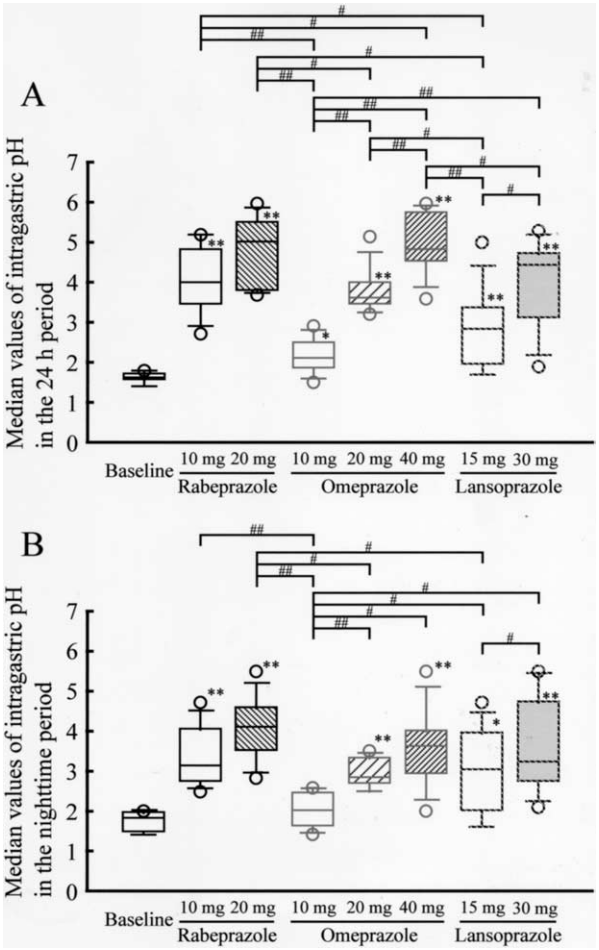

Fig 2. Box-whisker plots of median values of intragastric pH during 24-hour (**A**) and nighttime (10 PM to 6 AM) (**B**) periods without any medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole administered orally once daily after breakfast in *H pylori*–negative CYP2C19 homozygous extensive metabolizers (*1 asterisk*, $P < .05$; and *2 asterisks*, $P < .01$; versus baseline data; *1 pound sign*, $P < .05$; and *2 pound signs*, $P < .01$; between the 2 groups).

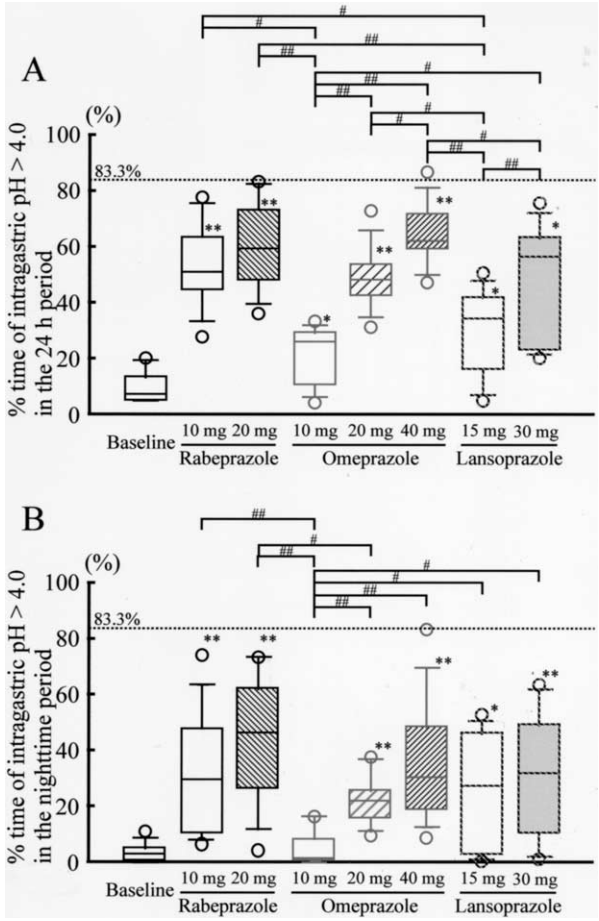

Fig 3. Box-whisker plots of percent of time that intragastric pH was above 4.0 during 24-hour (**A**) and nighttime (10 PM to 6 AM) (**B**) periods without any medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole administered orally once daily after breakfast in *H pylori*–negative CYP2C19 homozygous extensive metabolizers (*1 asterisk, P* $< .05$; and *2 asterisks, P* $< .01$; versus baseline data; *1 pound sign, P* $< .05$; and *2 pound signs, P* $< .01$; between the 2 groups).

Previous trial designs have involved a single comparator[21,22,50]; however, until now, no studies have been reported comparing the degrees of acid-suppressive effect among these PPIs at reduced and standard doses.

Evidence from previous pathophysiologic and clinical studies indicates that to protect the damaged esophageal mucosa from further damage and to facilitate healing within 8 weeks, therapy must attain a "critical pH threshold" for intragastric pH above 4.0 for 20 to 22 hours a day (ie, the percent of time that intragastric pH is above 4.0 should be more than 83.3% during the 24-hour period).[1,51] Furthermore, in patients with high-grade GERD, exposure of the esophagus to acid occurs frequently in the nighttime and daytime periods.[52] Therefore nocturnal gastric acid breakthrough should be considered when patients show resistance to PPI therapy.[49,52] However, in our study these 2 therapeutic goals were almost never achieved in CYP2C19 homozygous extensive metabolizers. For more potent acid control, particularly in the nighttime period, the addition of a bedtime H_2-RA to a PPI may be useful, at least

Table I. Median values of intragastric pH and percent of time that intragastric pH was above 4.0 during 24-hour and nighttime periods without any medication (baseline data) and with 10 mg and 20 mg rabeprazole; 10 mg, 20 mg, and 40 mg omeprazole; and 15 mg and 30 mg lansoprazole once daily after breakfast in *Helicobacter pylori*–negative CYP2C19 homozygous extensive metabolizers

Dose regimen	*Intragastric pH*	*% Time with intragastric pH >4.0*
24 h		
Baseline	1.6 (1.4-1.8)	7% (5%-20%)
Rabeprazole		
10 mg	4.0 (2.7-5.2)**	51% (28%-78%)**
20 mg	5.0 (3.7-6.0)**	59% (36%-83%)**
Omeprazole		
10 mg	2.1 (1.5-2.9)*	26% (4%-33%)*
20 mg	3.6 (3.2-5.2)**	48% (31%-73%)**
40 mg	4.8 (3.6-6.0)**	62% (47%-87%)**
Lansoprazole		
15 mg	2.8 (1.7-5.0)*	34% (5%-51%)*
30 mg	4.4 (1.9-5.3)*	56% (20%-76%)**
Nighttime (10 PM to 6 AM)		
Baseline	1.8 (1.4-2.0)	2% (0%-11%)
Rabeprazole		
10 mg	3.1 (2.5-4.7)**	29% (6%-74%)**
20 mg	4.1 (2.8-5.5)**	46% (4%-73%)**
Omeprazole		
10 mg	2.0 (1.4-2.6)	1% (0%-16%)
20 mg	2.8 (2.5-3.5)**	21% (9%-37%)**
40 mg	3.6 (2.0-5.5)**	30% (8%-83%)**
Lansoprazole		
15 mg	3.0 (1.6-4.7)*	27% (0%-53%)*
30 mg	3.2 (2.1-5.5)**	31% (1%-63%)**

Values are expressed as median and range.
*P <.05 and **P <.01, versus baseline data by Wilcoxon signed rank test.

for short-term therapy.[53,54] However, for long-term control in patients without *H pylori* infection, it might not be useful because of attenuated acid-suppressive effects during continuous administration of H_2-RAs.[55-60] Considering that PPIs have not shown the phenomenon of tolerance during continuous administration,[61] to achieve adequate acid suppression throughout a full day with a PPI alone in *H pylori*–negative CYP2C19 homozygous extensive metabolizers, 10 mg rabeprazole 4 times daily would need to be administered[62]; however, PPIs at a high dose or divided doses have not been approved as therapy for GERD in most countries, including Japan.

A "step-down" strategy (ie, initial therapy with a standard-dose PPI followed by maintenance therapy with a reduced-dose PPI) sometimes results in failure. In multicenter, randomized, controlled studies, the proportions of GERD patients in endoscopic remission were 35% with 10 mg omeprazole and 59% with 20 mg omeprazole after 6 months of maintenance therapy,[3] 50% with 10 mg omeprazole and 74% with 20 mg omeprazole after 12 months of maintenance therapy,[2] and 69% to 79% with 15 mg lansoprazole and 80% to 90% with 30 mg lansoprazole after 12 months of maintenance therapy.[4,10] On the other hand, endoscopic remission rates after 5 years of maintenance therapy were 90.2% with 10 mg rabeprazole and 88.5% with 20 mg rabeprazole, with no significant differences.[7] These clinical outcomes invite speculation concerning the greater differences in the acid-suppressive effects between 10 mg and 20 mg omeprazole, as well as between 15 mg and 30 mg lansoprazole, than between 10 mg and 20 mg rabeprazole. In our study significant differences were indeed observed in the median values of intragastric pH and the percent of time that pH was above 4.0 between 10 mg and 20 mg omeprazole, as well as between 15 mg and 30 mg lansoprazole, whereas no significant difference was observed between 10 mg and 20 mg rabeprazole in any time period. Moreover, 10 mg rabeprazole was significantly more

effective than 10 mg omeprazole and 15 mg lansoprazole. We previously clarified that the difference in acid-suppressive effects between 10 mg and 20 mg omeprazole is affected by the CYP2C19 genotype status: in homozygous extensive metabolizers the difference between 10 mg and 20 mg omeprazole in median values of the percent of time that pH was above 4.0 during the 24-hour period was statistically significant (23% versus 46%, $P < .05$), whereas no significant difference was observed in poor metabolizers (81% versus 90%).[21] These results indicate that reducing doses of omeprazole and lansoprazole results in a significant reduction of the acid-suppressive effect in CYP2C19 homozygous extensive metabolizers and allows for the possible recurrence of GERD. Therefore it may be necessary to test for CYP2C19 genotype status to determine the optimal dose of omeprazole or lansoprazole before a step-down or to carefully observe for any recurrence of clinical symptoms and for changes in endoscopic findings after the step-down to predict whether sufficient acid suppression has been achieved. On the other hand, these results also indicate that 10 mg rabeprazole has a potent acid-suppressive effect that is comparable to 20 mg rabeprazole in any CYP2C19 extensive metabolizer. Therefore, in the situation of a step-down (initial therapy with 20 mg rabeprazole is reduced to maintenance therapy with 10 mg rabeprazole), the genetic polymorphism might not need to be considered.

In conclusion, any PPI given once daily at reduced and standard doses failed to attain ideal acid suppression—that is, intragastric pH above 4.0 for more than 83.3% of a full day and inhibition of nocturnal gastric acid breakthrough. Therefore satisfactory clinical outcomes might not be expected in the initial therapy for GERD in *H pylori*–negative CYP2C19 homozygous extensive metabolizers. However, considering that there was no significant reduction of acid-suppressive effect in the case of a step-down with rabeprazole and that it had significantly greater acid-suppressive effects than other PPIs at a reduced dose, rabeprazole is the most appropriate drug for maintenance therapy in GERD patients who are *H pylori*–negative and CYP2C19 homozygous extensive metabolizers.

None of the authors has any conflict of interest to declare with respect to the contents of this manuscript.

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