PHARMACODYNAMICS AND DRUG ACTION

Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes

Background and Objective: **A concomitant dosage regimen of a histamine 2 receptor antagonist with a proton pump inhibitor (PPI) effectively decreases the incidence of nocturnal acid breakthrough, which is one of the problems encountered when acid-related diseases are treated with a PPI alone. We compared the effectiveness of an increased dosage regimen of rabeprazole with that of a concomitant dosage regimen of rabeprazole with famotidine, relative to cytochrome P450 (CYP) 2C19 genotype status, on nocturnal acid inhibition.**

Methods: **Fifteen *Helicobacter pylori*–negative volunteers, consisting of 5 homozygous extensive metabolizers (EMs), 6 heterozygous EMs, and 4 poor metabolizers (PMs) of CYP2C19, took 20 mg rabeprazole, 40 mg rabeprazole, and 20 mg rabeprazole plus 20 mg famotidine at bedtime (at 10 PM) for 8 days. The subjects then underwent 24-hour intragastric pH monitoring on day 8.**

Results: **For the 20-mg rabeprazole, 40-mg rabeprazole, and concomitant dosage regimens, the median percent times and ranges when nocturnal intragastric pH values were lower than 4.0 were 78.8% (47.5%-98.0%), 45.3% (29.0%-52.2%), and 15.5% (0.0%-40.8%), respectively, for homozygous EMs; 51.0% (7.0%-91.6%), 41.3% (33.0%-59.0%), and 18.5% (8.4%-31.9%), respectively, for heterozygous EMs; and 4.5% (2.0%-31.2%), 9.5% (0.0%-31.1%), and 9.3% (0.0%-14.7%), respectively, for PMs. Although significant differences in acid inhibition between the different CYP2C19 genotypes were observed when rabeprazole alone was given ($P = .016$ for 20 mg rabeprazole and $P = .023$ for 40 mg rabeprazole), such differences were not observed when famotidine was concomitantly given ($P = .206$).**

Conclusions: **The combination regimen of famotidine plus rabeprazole is more effective for nocturnal acid inhibition in homozygous and heterozygous EMs than the increased dosage regimen of rabeprazole. This concomitant therapy could be a rescue regimen for patients with nocturnal acid breakthrough refractory to a standard PPI therapy who are likely to be CYP2C19 EMs. (Clin Pharmacol Ther 2005;77:302-11.)**

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Proton pump inhibitors (PPIs) (eg, omeprazole, lansoprazole, rabeprazole, and pantoprazole) and histamine 2 receptor antagonists (H_2RAs) (eg, cimetidine, ranitidine, famotidine, and lafutidine) are now widely used as first-line therapy in treating gastroesophageal reflux disease (GERD).[1] Intraesophageal pH lower than

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4.0 directly correlates with the degree of esophageal mucosal injury; the severity of esophageal mucosal injury that occurs in GERD is linked with the duration of intragastric pH lower than 4.0.[2,3] A longer duration of intragastric pH greater than 4.0 leads to a shorter duration of intraesophageal pH lower than 4.0.[3] Therefore the inhibition of acid secretion for a longer period is the main strategy for treating GERD. Several authors have reported that the duration of intragastric pH lower than 4.0 during 24 hours should preferably be shortened to less than 2 to 4 hours (<16.7%).[3,4] PPIs potently suppress acid secretion during a 24-hour period but often fail to suppress it during the nighttime. Nocturnal gastric acid breakthrough, which is defined as the presence of an intragastric pH value lower than 4.0 for longer than 1 hour during the nocturnal time while a patient is undergoing a PPI treatment, is a therapeutic dilemma encountered during a PPI-based dosage regimen.[5] Therefore the development of an optimal treatment regimen for nocturnal acid inhibition should be considered clinically important when GERD is being treated.

Rabeprazole was reported to be reduced mainly via a nonenzymatic pathway, with minor cytochrome P450 (CYP) 2C19 involvement.[6,7] Therefore the pharmacokinetics and pharmacodynamics of rabeprazole are considered to be less affected by differences in CYP2C19 genotypes than those of omeprazole and lansoprazole, which are metabolized mainly by CYP2C19.[6-11] Recent reports, however, have confirmed that plasma rabeprazole concentrations differ significantly between CYP2C19 genotype groups: Those of poor metabolizers (PMs) are highest, those of heterozygous extensive metabolizers (EMs) are second highest, and those of homozygous EMs are lowest, as was observed with other PPIs.[9-12] Moreover, the CYP2C19 genotype–dependent difference in rabeprazole pharmacodynamics has been demonstrated.[13,14]

Increasing maximum plasma PPI concentration by increasing the PPI dosage regimen, as well as sustaining plasma PPI concentrations throughout a 24-hour period by use of a multiple-dosage regimen of a PPI, can effectively inhibit nocturnal acid secretion,[13,15-17] suggesting that nocturnal gastric acid breakthrough is associated with insufficient or lower plasma PPI concentrations, especially in homozygous and heterozygous EMs.[13,18,19]

Recently, a concomitant dosage regimen of a PPI with an H_2RA, such as famotidine or ranitidine, prescribed at bedtime, has been reported to inhibit nocturnal acid secretion more effectively than an increased dosage regimen of a PPI in short-term studies.[20-22] PPIs inhibit acid secretion by binding to activated H^+/K^+–adenosine triphosphatase (ATPase) in parietal cells, whereas H_2RAs competitively bind to the H_2 receptors on parietal cells and inhibit acid secretion mediated by histamine.[23,24] Moreover, H_2RAs, such as famotidine, are mainly excreted into urine without being metabolized by CYP2C19 or CYP3A4.[25] To our knowledge, however, there have been no reports comparing nocturnal acid inhibition resulting from an increased PPI dosage regimen with that of a concomitant H_2RA with a PPI dosage regimen relative to CYP2C19 genotype status. Therefore we aimed to compare the effects of once-daily bedtime dosing of 20 mg or 40 mg rabeprazole for 8 days with those of 20 mg rabeprazole plus 20 mg famotidine for 8 days on nocturnal acid secretion in relation to different CYP2C19 genotypes. We then intended to develop an optimal bedtime dosage regimen for the control of nocturnal acid secretion based on the CYP2C19 genotype status.

METHODS

Subjects and CYP2C19 genotyping. Blood samples were obtained from 44 healthy Japanese subjects after written informed consent was obtained from each subject. Deoxyribonucleic acid was extracted from each subject's leukocytes by use of a commercially available kit (IsoQuick; ORCA Research Inc, Bothell, Wash). Genotyping procedures for 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 use of a polymerase chain reaction–restriction fragment length polymorphism method with allele-specific primers.[26-28]

Of 40 subjects (14 homozygous EMs, 22 heterozygous EMs, and 4 PMs) without *Helicobacter pylori* infection determined by serologic testing (HM-CAP kit; Enteric Product, Inc, Westbury, NY) and carbon 13–urea breath testing, 5 homozygous EMs and 6 heterozygous EMs who were randomly selected and 4 PMs were invited to participate in the study (Table I). The subjects having the 3 different CYP2C19 genotypes exhibited no demographic differences in age, body weight, or height (Table I). None had consumed large amounts of alcohol or had a smoking habit. None had taken any drugs for at least 1 week before the study, nor did they take any during the study.

Study protocol. All subjects were given a once-daily dose of placebo, 20 mg or 40 mg rabeprazole (Pariet; Eisai Co Ltd, Tokyo, Japan), or 20 mg rabeprazole plus 20 mg famotidine (Gaster; Yamanouchi Pharmaceutical Co Ltd, Osaka, Japan) at 10 PM for 8 days in a randomized, double-blind, 4-way crossover fashion. On

Table I. Demographic characteristics of *H pylori*–negative healthy male volunteers with different *CYP2C19* genotypes

Study group	*Homozygous EMs (n = 5)*	*Heterozygous EMs (n = 6)*	*PMs (n = 4)*	*P value*
Genotype status	**1/*1* (n = 5)	**1/*2* (n = 4) **1/*3* (n = 2)	**2/*2* (n = 1) **3/*3* (n = 1) **2/*3* (n = 2)	
Age (y)	20.0 ± 0.6	20.3 ± 1.1	20.0 ± 0.7	.982
Body weight (kg)	61.0 ± 1.2	66.7 ± 2.0	67.0 ± 4.3	.242
Height (cm)	171.6 ± 1.0	176.7 ± 2.4	174.8 ± 3.5	.490

Age, body weight, and height are given as mean ± SE.
EM, Extensive metabolizer; PM, poor metabolizer; **1*, wild type; **2*, *CYP2C19*2* mutation in exon 5; **3*, *CYP2C19*3* mutation in exon 4.

day 8, 24-hour intragastric pH monitoring was performed in the subjects on each of the 4 regimens. All subjects were provided with 3 meals a day (breakfast [2100 kJ] at 8 AM, lunch [4284 kJ] at 12:30 PM, and supper [3570 kJ] at 6 PM). Mineral water was allowed as desired, but no other beverages were permitted. There was a washout period for at least 2 weeks between the 2 study periods. Written informed consent was again obtained from each subject before participation in the study. The protocol was approved in advance by the Human Institutional Review Board of the Hamamatsu University School of Medicine, Hamamatsu, Japan.

Twenty-four–hour intragastric pH monitoring. After overnight fasting, a glass pH electrode (Chemical Instruments Co Ltd, Tokyo, Japan) or an antimony pH electrode (Medtronic Functional Diagnostics, Inc, Shoreview, Minn) was inserted transnasally with the patient under local anesthesia and placed 5 cm distal to the cardia. Twenty-four–hour intragastric pH monitoring was performed on day 8 of each trial phase. The intragastric pH data were recorded with a Memory pH Meter (Chemical Instruments Co Ltd) or a Digitrapper MK III (Synectics Medical AB, Stockholm, Sweden). When the recordings were completed, the data were transferred to a computer and stored until analysis with the respective dedicated software programs.

Data analysis. The 24-hour intragastric pH monitoring period was divided into daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM). The median with the respective range of intragastric pH values and the percent of time when intragastric pH was lower than 4.0, which are widely used indices of acid secretion, were determined. The median pH values for the entire 24-hour period, nighttime period, and each hour were calculated from the raw pH values. Statistically significant differences in the median pH values and the median percent time of pH lower than 4.0 among the 3 CYP2C19 genotype groups were determined by the Mann-Whitney *U* test when a significant difference was obtained by the Kruskal-Wallis test. To determine whether these data would differ among the different dosing studies, the Wilcoxon signed rank test was used when significant differences were obtained by the Friedman test. All *P* values were 2-sided, and $P < .05$ was taken to indicate statistical significance.

RESULTS

Twenty-four–hour intragastric pH–time profiles. The median daytime pH-time profiles for homozygous EMs and heterozygous EMs were fairly similar for the 3 regimens (Fig 1, *A* and *B*). The median nocturnal pH-time profiles attained by the 3 regimens, however, differed as follows: Nocturnal pH greater than 4.0 was attained with a concomitant regimen of 20 mg rabeprazole plus 20 mg famotidine but not with either 20 mg or 40 mg rabeprazole alone in homozygous and heterozygous EMs. In PMs the median pH-time profiles attained by the 3 regimens over the 24-hour period were similar to each other and pH values were greater than 4.0 throughout the 24-hour period for all 3 regimens (Fig 1, *C*).

Intragastric pH during nocturnal and 24-hour periods. In homozygous EMs, the median nocturnal pH values attained with 40 mg rabeprazole alone and the concomitant regimen with 20 mg rabeprazole plus 20 mg famotidine were 4.4 and 6.1, respectively. These were significantly higher than the value attained with 20 mg rabeprazole (2.4) (both $P = .043$) (Fig 2, *A*, *left*). In heterozygous EMs the median pH value reached 5.9 (Fig 2, *A*, *middle*) for the concomitant regimen, which was significantly higher than the value attained with 40 mg rabeprazole (4.7) or 20 mg rabeprazole (4.6) (both $P = .043$). On the other hand, in PMs the median pH

value attained by all 3 regimens was greater than 6.0 (Fig 2, *A*, *right*).

During the 24-hour period, the median pH value attained with 20 mg rabeprazole in homozygous EMs was 3.8, which was significantly lower than that attained with 40 mg rabeprazole (4.6) (Fig 2, *B*, *left*). In heterozygous EMs and PMs the median pH values attained by use of the 3 regimens were around 5.0 and 6.0, respectively (Fig 2, *B*, *middle* and *right*).

Percent time of intragastric pH lower than 4.0 during nocturnal and 24-hour periods. In homozygous EMs the median percent times when the nocturnal pH was lower than 4.0 during rabeprazole treatment at doses of 20 mg and 40 mg were 78.8% and 45.3%, respectively, which appeared to be insufficient (>16.7%)[3] (Fig 3, *A*, *left*). The value attained during the concomitant regimen with 20 mg rabeprazole plus 20 mg famotidine, however, was significantly reduced to 15.5% (both $P = .043$). In heterozygous EMs, when rabeprazole was increased from 20 mg to 40 mg, no significant decrease in median percent time with a nocturnal pH value lower than 4.0 was observed (from 51.0% to 41.3%). With the concomitant dosage, however, this was significantly reduced to 18.5% ($P = .043$ and .028) (Fig 3, *A*, *middle*). In PMs the values attained with 20 mg or 40 mg rabeprazole and the concomitant regimen were 4.5% or 9.5% and 9.3%, respectively. No significant difference was observed between the 3 regimens (Fig 3, *A*, *right*).

During the 24-hour period, in homozygous EMs, the median percent time of pH lower than 4.0 was 60.0% for 20 mg rabeprazole, 42.0% for 40 mg rabeprazole, and 28.8% for the concomitant dosage regimen with 20 mg rabeprazole plus 20 mg famotidine ($P = .196$) (Fig 3, *B*, *left*). In heterozygous EMs this value did not differ among the 3 different regimens and remained around 40% ($P = .751$) (Fig 3, *B*, *middle*). In PMs, however, the values attained with 20 mg or 40 mg rabeprazole and the concomitant regimen were 10.5% or 13.0% and 25.1%, respectively ($P = .794$) (Fig 3, *B*, *right*).

With 20 mg or 40 mg rabeprazole, the median pH values or the median percent time for pH lower than 4.0 during the 24-hour and nighttime periods in PMs were significantly higher or shorter, respectively, than those in homozygous and heterozygous EMs (all $P < .05$) (Table II). With 20 mg or 40 mg rabeprazole, there were no significant differences in the parameters for gastric acid inhibition between homozygous EMs and heterozygous EMs. The concomitant regimen, however, exhibited no significant differences in the median pH values ($P = .2351$ during the 24-hour periods and $P = .9347$ during the nighttime periods) and the median

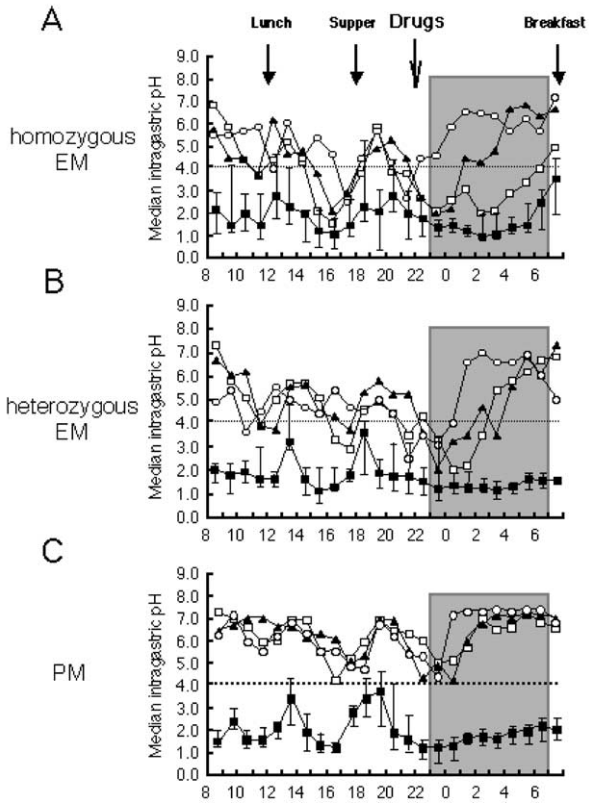

Fig 1. Median 24-hour pH-time profiles on day 8 of dosages (at 10 PM) of placebo (*solid squares*), 20 mg (*open squares*) and 40 mg (*triangles*) rabeprazole alone, and 20 mg rabeprazole plus 20 mg famotidine (*circles*) for different CYP2C19 genotype groups. In homozygous extensive metabolizers (EMs) and heterozygous EMs, the median nocturnal pH attained with 20 mg rabeprazole plus 20 mg famotidine was highest for all of the regimens (*shaded area* in **A** and **B**). In poor metabolizers (PMs), median pH-time profiles greater than 4.0 over a 24-hour period were attained with all 3 regimens (**C**). The interquartile ranges are indicated as the *whiskers*, and those have not been added to the other data points to preserve clarity, but the variances were similar in other sets of data.

percent time of intragastric pH lower than 4.0 ($P = .0851$ during the 24-hour periods and $P = .2064$ during the nighttime periods) among the 3 CYP2C19 genotype groups.

Incidence of nocturnal gastric acid breakthrough. For treatment with either 20 mg or 40 mg rabeprazole, the incidence of nocturnal gastric acid breakthrough in PMs was 25% (1/4), which was lower than that for heterozygous EMs (both 83% [5/6]) and homozygous EMs (both 100% [5/5]) (both $P = .150$) (Table III). The respective incidence

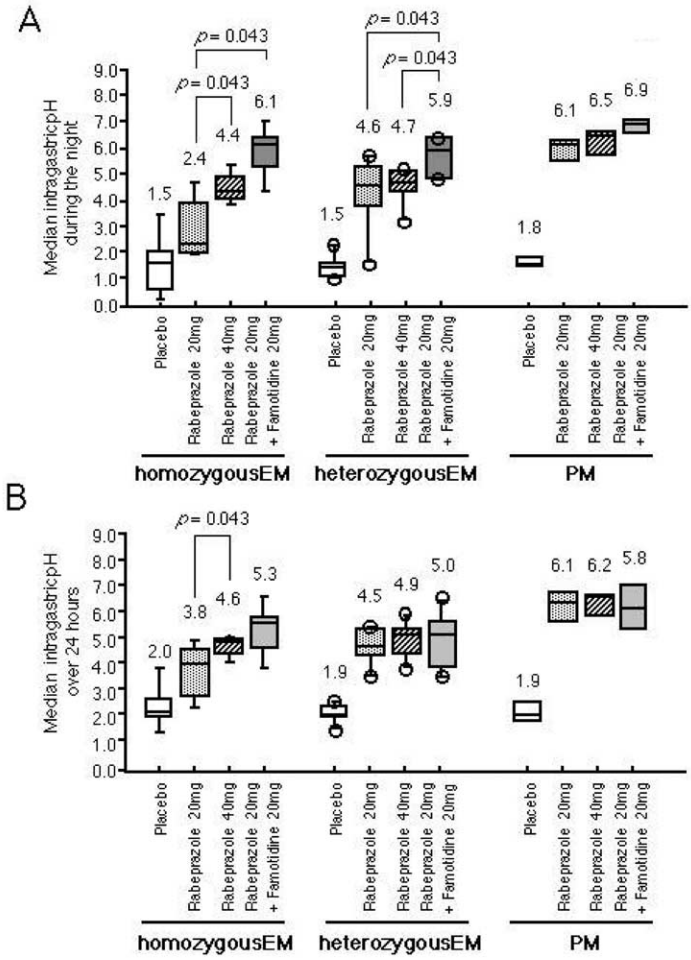

Fig 2. Median pH values during nighttime (**A**) and 24-hour period (**B**) for 20 mg and 40 mg rabeprazole and 20 mg rabeprazole plus 20 mg famotidine for different CYP2C19 genotype groups. In homozygous and heterozygous EMs, the median nocturnal pH attained with 20 mg rabeprazole was significantly lower (**A**). For PMs pH values attained for all regimens were greater than 6.0. In homozygous EMs the median pH attained with 20 mg rabeprazole during the 24-hour period was significantly lower than that with 40 mg rabeprazole (**B**). In heterozygous EMs and PMs, the pH values for the 3 regimens were similar to each other and were around 5.0 and 6.0, respectively.

of nocturnal gastric acid breakthrough attained by the concomitant dosage regimen decreased to 0% (0/4) in PMs, 33.3% (2/6) in heterozygous EMs, and 40% (2/5) in homozygous EMs ($P = .570$).

DISCUSSION

We demonstrated that the concomitant dosage regimen of 20 mg rabeprazole with 20 mg famotidine given at bedtime for 8 days significantly increased the median nocturnal intragastric pH values and decreased the median percent time with a nocturnal intragastric pH value lower than 4.0, as compared with treatment with 20 mg or 40 mg rabeprazole at bedtime for 8 days, in homozygous EMs and heterozygous EMs. This concomitant treatment was also effective in decreasing the incidence of nocturnal gastric acid breakthrough compared with the increased rabeprazole dosage regimen. In EMs the increased rabeprazole dosage regimen could not yield sufficient nocturnal acid inhibition. On the other hand, in PMs the nocturnal acid inhibition achieved by 20 mg or 40 mg rabeprazole and the concomitant regimen was fairly similar and sufficient. Moreover, we discovered that

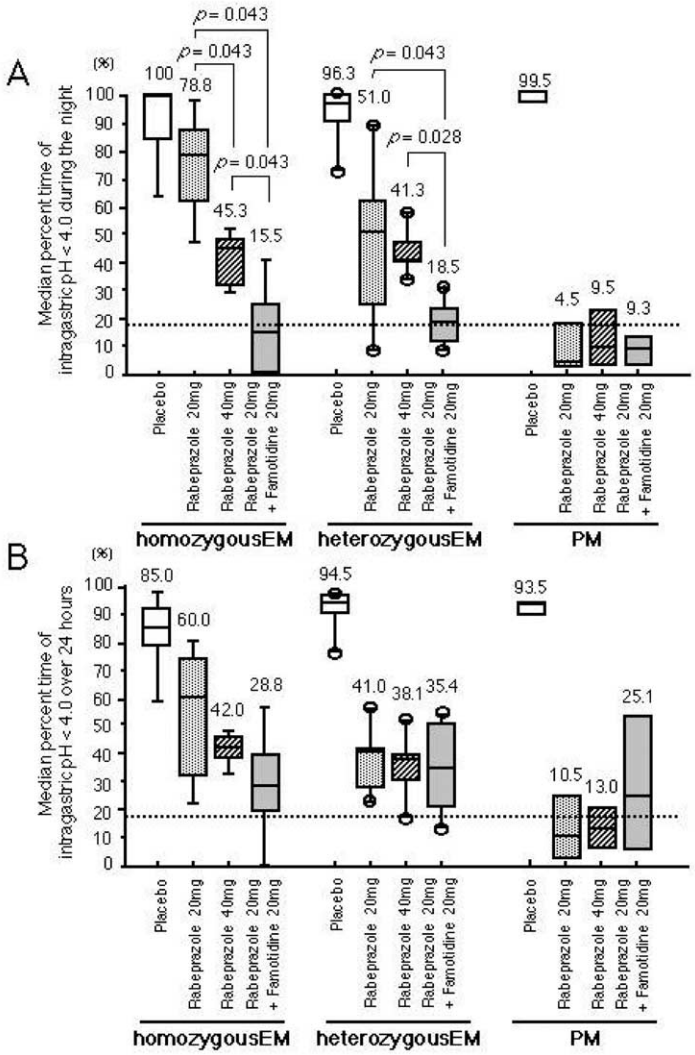

Fig 3. Median percent time of pH lower than 4.0 during nighttime (**A**) and 24-hour periods (**B**) as a function of CYP2C19 genotype. In homozygous and heterozygous EMs, the median percent time of pH lower than 4.0 during the nighttime with the concomitant regimen (20 mg rabeprazole plus 20 mg famotidine) was significantly decreased compared with that attained with rabeprazole alone (**A**). In PMs the pharmacodynamic parameter attained with the concomitant regimen was almost the same as that attained with 20 or 40 mg rabeprazole (**A**). In homozygous and heterozygous EMs the median percent time of pH lower than 4.0 over the 24-hour period for all attained regimens was greater than 20% (**B**). In PMs, however, rabeprazole alone (20 mg and 40 mg), not the concomitant regimen, was sufficient to maintain the median percent time of intragastric pH lower than 4.0 (ie, $<16.7\%$).

the acid inhibition attained by rabeprazole alone significantly depended on the CYP2C19 genotype status, as observed with other PPIs,[6,9,12,18,29] and that this CYP2C19 genotype–dependent difference was not observed during the concomitant regimen. On the basis of these observations, we wish to propose a therapeutic strategy for overcoming nocturnal gastric acid breakthrough by use of rabeprazole with or without famotidine in relation to the CYP2C19 genotype status as follows: concomitant treatment with 20 mg famotidine plus 20 mg rabeprazole for EMs and treatment with 20 mg rabeprazole alone for PMs.

Table II. Median intragastric pH values and median percent time of intragastric pH lower than 4.0 during nighttime and 24-hour periods with different dosage regimens as a function of *CYP2C19* genotype status

	Median intragastric pH			*Median percent time of pH < 4.0*		
Dosage regimen	*Homozygous EMs*	*Heterozygous EMs*	*PMs*	*Homozygous EMs*	*Heterozygous EMs*	*PMs*
Nighttime						
Placebo	1.5 (0.3-3.5)	1.5 (1.1-2.4)	1.8 (1.5-2.1)	100% (64.0%-100%)	96.3% (71.2%-100%)	99.5% (93.3%-100%)
Rabeprazole, 20 mg	2.4* (2.0-4.7)	4.6* (1.5-5.7)	6.1 (5.1-6.6)	78.8%* (47.5%-98.0%)	51.0%* (7.0%-91.6%)	4.5% (2.0%-31.2%)
Rabeprazole, 40 mg	4.4* (3.9-5.4)	4.7* (3.2-5.3)	6.5 (5.1-6.7)	45.3%* (29.0%-52.2%)	41.3%* (33.0%-59.0%)	9.5% (4.0%-31.1%)
Concomitant dosage	6.1 (4.4-7.0)	5.9* (4.8-6.4)	6.9 (6.3-7.1)	15.5% (0.0%-40.8%)	18.5% (8.4%-31.9%)	9.3% (0.0%-14.7%)
24 h						
Placebo	2.0 (1.2-3.6)	1.9 (1.3-2.4)	1.9 (1.5-2.8)	85.0% (58.0%-97.0%)	94.5% (75.5%-98.0%)	93.5% (88.0%-95.0%)
Rabeprazole, 20 mg	3.8* (2.1-4.7)	4.5* (3.3-5.1)	6.1 (5.1-6.5)	60.0%* (22.0%-80.1%)	41.0%* (22.0%-57.8%)	10.5% (3.0%-31.4%)
Rabeprazole, 40 mg	4.6* (3.9-4.8)	4.9* (3.6-5.8)	6.1 (5.1-6.4)	42.0%* (32.7%-48.2%)	38.1%* (16.0%-53.2%)	13.0% (3.0%-24.8%)
Concomitant dosage	5.3 (3.6-6.3)	5.0 (3.3-6.3)	5.8 (4.7-7.2)	28.8% (0.0%-56.2%)	35.4% (13.2%-54.7%)	25.1% (1.0%-67.0%)

Date are given as median and range.
*$P < .05$ (versus PM) by use of the Mann-Whitney U test when a significant difference was observed by use of the Kruskal-Wallis test.

Table III. Incidence of nocturnal gastric acid breakthrough by 3 different regimens as a function of *CYP2C19* genotype status

	Incidence rate of nocturnal gastric acid breakthrough				
Treatment	*Total*	*Homozygous EMs*	*Heterozygous EMs*	*PMs*	*P value*
Rabeprazole, 20 mg	11/15 (73%)	5/5 (100%)	5/6 (83%)	1/4 (25%)	.150
Rabeprazole, 40 mg	11/15 (73%)	5/5 (100%)	5/6 (83%)	1/4 (25%)	.150
Rabeprazole, 20 mg, plus famotidine, 20 mg	4/15 (27%)	2/5 (40%)	2/6 (33%)	0/4 (0%)	.570

Acid secretion increases during the nighttime, peaking around midnight.[30-32] The major stimulator of nocturnal acid secretion is histamine, and therefore an H_2RA may effectively inhibit nocturnal acid secretion.[12,30] In patients with high-grade GERD, which generally tends to be refractory to standard PPI therapy, 24-hour intraesophageal pH monitoring studies have revealed frequent reflux episodes throughout the 24-hour period, especially during the nighttime.[20,33] Therefore the concomitant regimen of a PPI plus an H_2RA may be the optimal treatment for patients with high-grade GERD.[22] Moreover, the addition of an H_2RA to a PPI inhibits acid secretion without an increase in the messenger ribonucleic acid for the H^+/K^+-ATPase in parietal cells in a short period.[34] This combinatory regimen may be more effective than the increased dosage of a PPI alone, which will induce the overexpression of messenger ribonucleic acid, affecting H^+/K^+-ATPase. Indeed, we observed that the nocturnal intragastric pH values obtained with the concomitant dosage were higher than those obtained with only the increased dosage of rabeprazole in EMs.

The advantage of H_2RAs is that their metabolism is not influenced by CYP2C19 genotype status.[12,25] Famotidine and other H_2RAs are excreted into urine predominantly in the unchanged form. Moreover, famoti-

dine's nocturnal acid inhibition in homozygous EMs was significantly more potent than that of lansoprazole.[12] In our study the acid inhibition attained by the concomitant treatment of rabeprazole plus famotidine did not appear to differ among the 3 CYP2C19 genotype groups. Interestingly, the effect of the concomitant dosage was much more evident in EMs than in PMs, because sufficient acid inhibition could be achieved in PMs with rabeprazole alone. Although the advantages of using concomitant treatment have been elucidated in this study, which was performed in Japanese subjects, it may be more clinically significant for white subjects. This is because the frequency of homozygous EMs in the white population (70%-75%) is much greater than in Asian populations including Japanese (30%-40%).[28,35,36]

The concomitant dosage of an H_2RA with a PPI has been reported to be effective for patients with GERD who are refractory to treatment with a PPI alone.[22] However, there are some patients who remain refractory to the concomitant dosage regimen.[20-22,37-39] As shown in this study, the concomitant dosage could not sufficiently inhibit acid production during the daytime. The percent time of intragastric pH lower than 4.0 during the 24 hours of the concomitant regimen was 28.8% for homozygous EMs, 35.4% for heterozygous EMs, and 25.1% for PMs (>16.7%).[3] Therefore we assume that GERD patients who are refractory to the concomitant dosage regimen would require another additional advanced treatment for sufficient acid inhibition throughout a 24-hour period, such as more frequent PPI doses (eg, 10 mg rabeprazole 4 times daily and 30 mg lansoprazole 4 times daily).[13,17]

The development of tolerance during treatment with an H_2RA has been documented as a disadvantage of H_2RA therapy.[40-42] After only 2 to 5 posttreatment days, H_2RA acid inhibition becomes significantly decreased as a result of the development of tolerance, especially for the treatment with a higher dose.[40,41] Moreover, the preventive effects of nocturnal gastric acid breakthrough are also significantly reduced after concomitant treatment for 1 to 2 weeks.[37-39] Therefore whether the control of nocturnal acid inhibition by the use of an H_2RA would be sustained over a long-term period is now controversial, and further studies are necessary to clarify this issue.[37-39]

In conclusion, this study suggests that the CYP2C19 genotyping test appears to be a useful tool for determining the optimal treatment for acid-related diseases that require intensive nocturnal acid inhibition. If CYP2C19 genotype status is determined before treatment is initiated, an optimal dosage regimen consisting of a PPI with or without an H_2RA can be selected on the basis of pharmacogenetic or pharmacogenomic status. We wish to recommend the following dosage regimens for patients who require intensive control of nocturnal acidity: 20 mg rabeprazole for PMs and a concomitant dosage of 20 mg rabeprazole plus 20 mg famotidine for heterozygous and homozygous CYP2C19 EMs. This pharmacogenetics-based strategy is expected to increase the cure rates of GERD when used as the initial treatment. However, the clinical usefulness of our proposed therapeutic strategy should be verified in GERD patients under the appropriate study design in the future.

None of the authors has a conflict of interest related to this study.

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