

# Intra-gastric pH following single oral administrations of rabeprazole and esomeprazole: double-blind cross-over comparison

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(Received 28 February, 2014; Accepted 14 May, 2014; Published online 4 October, 2014)

Comparisons between the acid inhibitory effects of rabeprazole and esomeprazole after single oral administration with standard doses have not been previously presented. We examined intra-gastric pH after oral administrations of these two proton pump inhibitors using 24-h pH monitoring. Fifty-four normal volunteers not infected by *Helicobacter pylori* were investigated. Using a cross-over design, we administered 10 mg of rabeprazole or 20 mg of esomeprazole in 27 at 30 min after supper and in the remaining 27 subjects at 15 min before supper, and performed 24-h pH monitoring. Intra-gastric pH data were nearly identical when the proton pump inhibitors were taken after meals. Even if the data were compared in different CYP2C19 genotypes, rabeprazole and esomeprazole did not show the difference. In poor metabolizer, both of the drugs showed stronger acid inhibition. When taken before meals, intra-gastric pH after esomeprazole administration was slightly but not significantly higher than that observed after rabeprazole administration not only in daytime but also in nighttime period. In conclusion, rabeprazole and esomeprazole were similarly effective when administered after a meal.

**Key Words:** intra-gastric pH, rabeprazole, esomeprazole, double-blind, cross-over

Proton pump inhibitors (PPIs) potently inhibit gastric acid secretion, and are widely used for prevention and treatment of various acid-related diseases including peptic ulcers and gastroesophageal reflux diseases. Although their acid inhibitor potency is far stronger than that of histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs), PPIs are reported to have some weak points in comparison with those drugs.<sup>(1-3)</sup>

A disadvantage of the acid inhibitory effect of PPIs is the strong influence of CYP2C19, a hepatic drug metabolizing enzyme that degrades PPIs.<sup>(4)</sup> In patients with high activity of the CYP2C19 enzyme (extensive metabolizers), the effect of PPI administration is not adequately strong, because of enzymatic degradation. On

the other hand, in patients with a low CYP2C19 enzyme activity (poor metabolizers), the acid inhibiting effect of PPIs can be too strong. Another disadvantage is slow onset of the acid inhibitory effect after PPI administration.<sup>(1,2)</sup>

To improve these weak points, new types of PPIs have been developed and are widely used. Rabeprazole is a new type of PPI that is not strongly influenced by CYP2C19 enzyme activity,<sup>(4)</sup> because it is not mainly degraded by CYP2C19.<sup>(5)</sup> In addition, this drug is reported to inhibit acid secretion more quickly than first generation PPIs including omeprazole and lansoprazole.<sup>(6)</sup> Another agent is esomeprazole, an S-isomer of omeprazole that is a mixture of S- and R-isomers. Esomeprazole has also been reported to not be effectively degraded by CYP2C19 and its effect is not strongly influenced by its enzyme activity.<sup>(7-9)</sup>

The acid suppressing effects of rabeprazole (20 mg) and esomeprazole (40 mg) have been investigated, with those of the latter reported to be equal or superior to the former.<sup>(10-13)</sup> The standard doses of rabeprazole and esomeprazole in Japan are 10 and 20 mg, respectively, per day. Those PPIs at those doses have not been directly compared in regard to quickness of acid inhibition and acid inhibitory potency in cases with different CYP2C19 enzyme activities.<sup>(14,15)</sup> It is considered that intra-gastric pH monitoring soon after acute single administration of a PPI is an ideal experimental design to investigate its quick acid inhibitory effects.

In the present study, a single standard dose of rabeprazole or esomeprazole was administered to normal volunteers in a multi-center double-blind randomized prospective study with a cross-over design and their effects on intra-gastric pH were compared.

## Materials and Methods

**Subjects.** Fifty-seven healthy volunteers were enrolled at 9 university hospitals; Shimane University, Hokkaido University

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**Table 1.** Clinical characteristics of subjects

	PPI administration	
	Before meal	After meal
Number of cases	27	27
Male/female	16/11	15/12
Age (years)	25.2 ± 4.9*	23.6 ± 3.0*
Height (cm)	166.8 ± 10.2*	168.3 ± 7.5*
Weight (kg)	58.4 ± 10.7*	60.0 ± 10.7*
BMI	20.8 ± 2.2*	21.0 ± 2.3*
Alcoholic drink (+/-/+)	8/15/4	4/19/4
Smoking (+/-/+/?)	1/20/4/2	0/21/4/2
<i>H. pylori</i> (+/-)	0/27	0/27
CYP2C19 (IM/PM/RM)	11/8/8	17/5/5

\*mean ± SD.

Hospital, Gunma University Hospital, Nippon Medical School, Yokohama City University Hospital, Hamamatsu University School of Medicine, Osaka City University, Osaka Medical College, and Saga Medical School. The protocol utilized was approved by the institutional ethical committees of the participating institutions.

The clinical characteristics of the subjects are shown in Table 1. Their mean age was in the 20s and none of the subjects was infected by *Helicobacter pylori* (*H. pylori*), which was determined by testing for the presence of the *H. pylori* antibody in serum and urine samples. The CYP2C19 genotype was tested by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, as previously reported.<sup>(4)</sup>

**pH monitoring.** Twenty-nine of the 57 enrolled volunteers were randomly enrolled in the pre-meal PPI administration protocol. The subjects were investigated by pH monitoring twice, once with 10 mg of rabeprazole and once with 20 mg of esomeprazole. The PPIs were delivered in identical opaque gelatin capsules and discrimination between them was impossible during the study period. The identical opaque gelatin capsules containing 10 mg rabeprazole or 20 mg esomeprazole were prepared by an author pharmacist (KN) and packaged in marked bags, and then delivered to each participating hospital. The key code of the drugs was kept by KN and opened firstly after fixing the final pH data. The order of administration was randomly determined for each subject. The 2 pH monitoring examinations were separated by at least a 1-week interval. An intra-gastric pH monitoring sensor catheter (Zenetics Medical, Salt Lake City, UT) was introduced into the gastric body and monitoring was started at 17:00, as previously reported.<sup>(16,17)</sup> A single oral dose of the PPI was administered at 15 min before supper, at 18:45. The subjects started eating their supper (carbohydrates 112.8 g, protein 16.3 g, fat 27.3 g, calories 762 kcal) at 19:00 and were asked to finish within 30 min. The subjects were then requested to lie on their bed from 23:00 to 7:00 next morning. Breakfast (carbohydrates 34 g, protein 5.8 g, fat 2.8 g, calories 85 kcal) and lunch (carbohydrates 74.4 g, protein 17.1 g, fat 11.4 g, calories 531 kcal) were also consumed within 30 min, starting at 8:00 and 12:00, respectively. Intra-gastric pH monitoring was terminated at 17:00. The remaining 28 subjects were enrolled in the postprandial PPI administration protocol group. All conditions were the same as above, except that rabeprazole or esomeprazole was administered orally 30 min after the end of supper at 20:00. In the postprandial administration protocol, the supper (carbohydrate 52.8 g, protein 8.8 g, fat 9.2 g, calorie 330 kcal) and breakfast (carbohydrate 94 g, protein 13.3 g, fat 20.9 g, calorie 617 kcal) were also slightly different from those used in the pre-meal administration protocol.

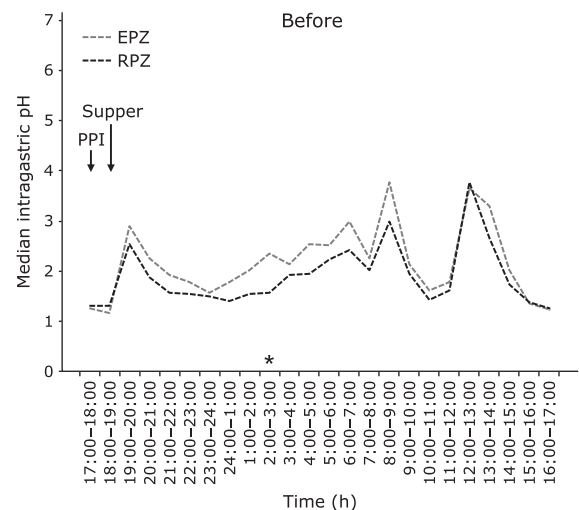
Median pH for each monitored hour and the percentage of time at which intra-gastric pH was below 4.0 were calculated for the total 24-h period, as well as the daytime (7:00–23:00) and nighttime (23:00–7:00) periods.

**Statistical analysis.** Statistical analysis was performed using a Wilcoxon signed rank test when results of a Friedman test showed significant differences. The chronological data shown in Fig. 1, 3, 4 and 6 were analyzed by linear mixed models. A *p* value of <0.05 was considered to be significant. The sample size of the study was calculated based on the previous studies comparing 40 mg esomeprazole and 20 mg rabeprazole on their first administration day.<sup>(10,12)</sup> Hunfeld *et al.*<sup>(10)</sup> calculated the number of necessary subjects as 18 based on parametric assumption and found the statistically significant results in their study. Warrington *et al.*<sup>(12)</sup> enrolled 24 healthy subjects in their study. Therefore, in this study, 27 healthy subjects were enrolled in two different protocols (administration before or after a meal).

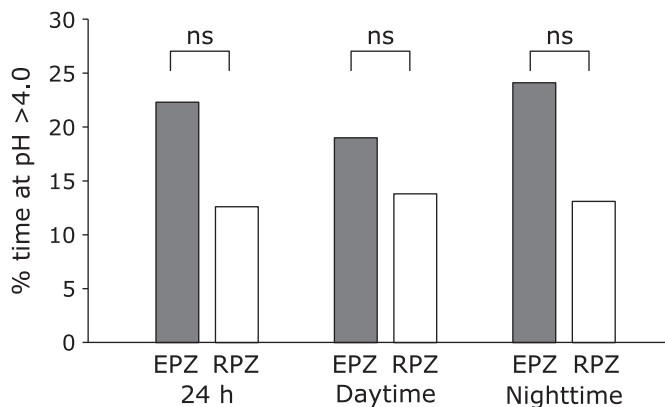
## Results

Of the 57 enrolled subjects, 2 in the preprandial administration group and 1 in the postprandial group were not analyzed because of intolerance to the second pH monitoring examination. No adverse event occurred during pH monitoring. There were no significant differences in regard to gender, age, height, body weight, BMI, and CYP2C19 genotypes between the administration protocol groups (Table 1).

When administered before the meal, the median intra-gastric pH after esomeprazole administration tended to be higher than after rabeprazole administration (Fig. 1), whereas intra-gastric pH in the 2:00–3:00 time period was significantly higher after esomeprazole administration. At the other time points, there were no significant differences. We also calculated percent time of intra-gastric pH >4.0 over the 24-h period, as well as during the daytime and nighttime periods. Again, esomeprazole tended to show a stronger acid inhibitory effect, though differences with rabeprazole were not significant (Fig. 2). When the data was separately calculated for different CYP2C19 genotypes, esomeprazole raised intra-gastric pH more effectively in rapid metabolizers at 4 time points in 24-h observation period (Fig. 3), while there was no apparent difference between intra-gastric pH between rabeprazole and esomeprazole in the intermediate and poor metabolizers, except at a single time point in poor metabolizers.



**Fig. 1.** Median intra-gastric pH for 24 h after a single preprandial oral administration of 10 mg of rabeprazole (black line) or 20 mg of esomeprazole (gray line). Using a cross-over design, 27 *H. pylori* uninfected subjects were studied with at least a 1-week interval between the rabeprazole and esomeprazole administrations. At only 1 time point measurement, esomeprazole raised intra-gastric pH to a significantly higher level than rabeprazole, while there were no significant differences found for the other time points. \**p*<0.05, statistically significant.



**Fig. 2.** Median % time at pH >4.0 during 24-h period after single preprandial oral administration of 10 mg of rabeprazole (white column) or 20 mg of esomeprazole (gray column) in 27 subjects. Although esomeprazole tended to elevate intra-gastric pH to a greater degree, there were no significant differences between the PPIs regarding acid inhibitory effects. RPZ, rabeprazole; EPZ, esomeprazole.

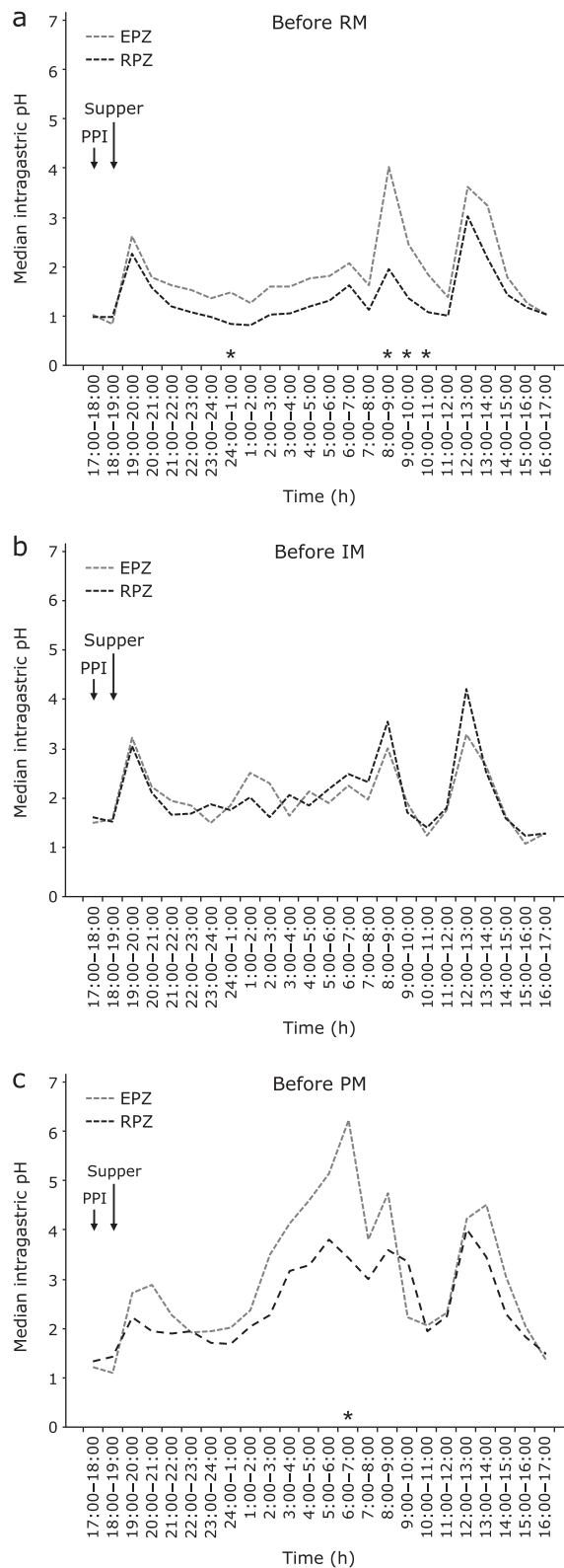
When the PPIs were administered after meals, there were no apparent differences in median intra-gastric pH at any time point after either administration (Fig. 4). Furthermore, after calculating percent time of intra-gastric pH >4.0, there were no differences found during the daytime and nighttime periods (Fig. 5). Median intra-gastric pH was also calculated based on CYP2C19 genotype, and compared between rabeprazole and esomeprazole, with no significant difference found, except at a single time point in poor metabolizers (Fig. 6).

## Discussion

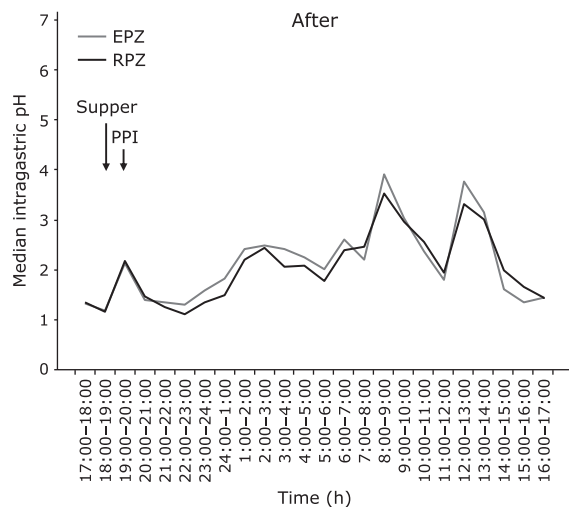
The present results show that the acid inhibitory effects of 10 mg of rabeprazole and 20 mg of esomeprazole after single oral doses were similarly potent, especially when administered after meals. Four kinds of PPIs, omeprazole, lansoprazole, rabeprazole, and esomeprazole, are available for clinical practice in Japan, which can be divided into 2 groups based on their degradability by the hepatic drug metabolizing enzyme CYP2C19.<sup>(4,18,19)</sup> Omeprazole and lansoprazole are easily degraded by CYP2C19, while rabeprazole and esomeprazole are not. Asian individuals are known to have heterogeneous CYP2C19 enzyme activity, as 30% are extensive metabolizers with high enzyme activity, 20% are poor metabolizers with low enzyme activity, and the remaining 50% are intermediate metabolizers.<sup>(20-22)</sup> Therefore, different from western countries, the acid inhibitory effects of omeprazole and lansoprazole are known to be diverse among individuals.<sup>(4,19)</sup> In cases with a high level of CYP2C19 enzyme activity, the acid inhibitory effects of these drugs are expected to be limited. To improve uncertainty, the more stable PPIs rabeprazole and esomeprazole are increasingly used in clinical practice for Japanese patients, with standard oral doses of 10 and 20 mg, respectively.

Rabeprazole is a newly developed racemic mixture compound reported to resist CYP2C19 degradation,<sup>(5)</sup> while esomeprazole is an S-isomer of omeprazole and similarly resistant to CYP2C19. Therefore, these PPIs are considered to have a more consistent acid inhibitory effect irrespective of CYP2C19 enzyme activity.<sup>(7-9)</sup> However, that of esomeprazole is considered to become sub-maximal when the drug is administered after a meal.

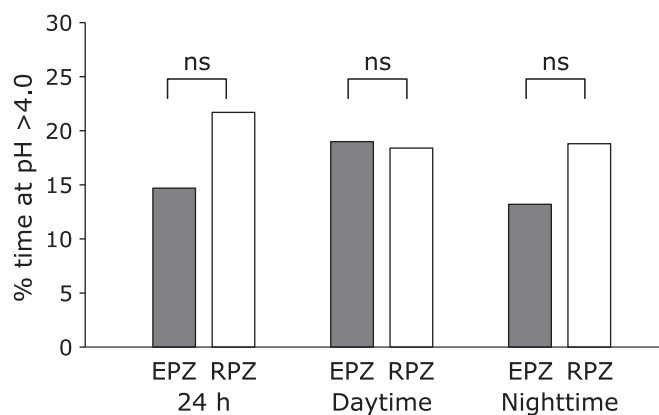
There are 2 possible mechanisms regarding this weak point of esomeprazole to consider, decreased absorption and incomplete activation. The plasma concentration of esomeprazole was investigated and compared when administered during fasting and after meals.<sup>(23,24)</sup> Those results clarified that the plasma concentration of esomeprazole was higher when administered during fasting,



**Fig. 3.** Median intra-gastric pH during 24-h period after single preprandial oral administration of 10 mg of rabeprazole (black lines) or 20 mg of esomeprazole (gray lines) in (a) rapid metabolizers ( $n = 8$ ), (b) intermediate metabolizers ( $n = 11$ ), and (c) poor metabolizers ( $n = 8$ ) of CYP2C19. In the rapid metabolizers, intra-gastric pH after administration of esomeprazole was significantly higher at 4 different time points as compared to rabeprazole. In intermediate and poor metabolizers, no significant and only one point significant differences were found, respectively. \* $p < 0.05$ , statistically significant.



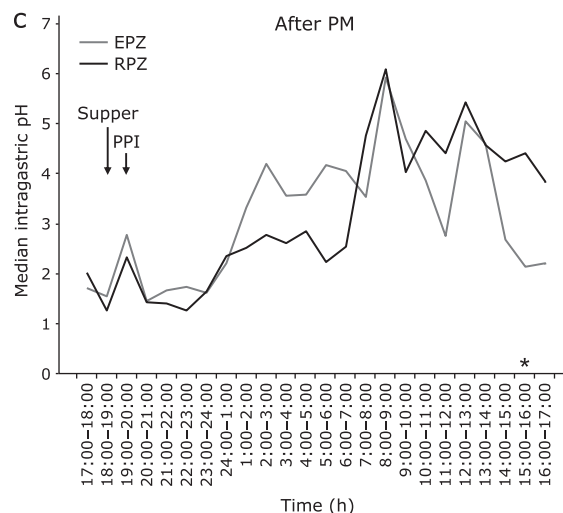
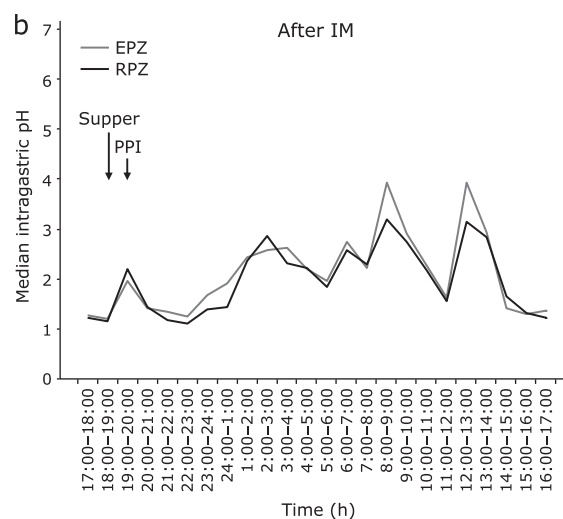
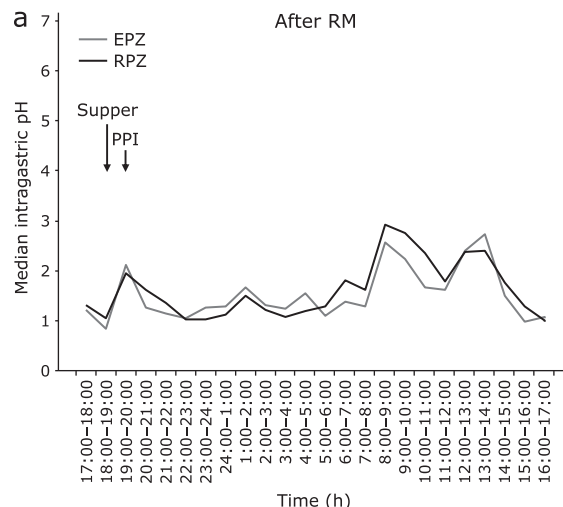
**Fig. 4.** Median intra-gastric pH during 24-h period after single post-prandial oral administration of 10 mg of rabeprazole (black line) or 20 mg of esomeprazole (gray line). Using a cross-over design, 27 *H. pylori* uninfected subjects were studied with at least a 1-week interval between the rabeprazole and esomeprazole administrations. Intra-gastric pH values after administrations of rabeprazole and esomeprazole were nearly identical.



**Fig. 5.** Median % time at pH >4.0 during 24-h period after single post-prandial oral administration of 10 mg of rabeprazole (white column) or 20 mg of esomeprazole (gray column) in 27 subjects. There were no differences between esomeprazole and rabeprazole. RPZ, rabeprazole; EPZ, esomeprazole.

though the precise mechanism related to that difference is not clear. All PPIs need to be activated by the acidic environment in the secretory canaliculi of parietal cells.<sup>(25)</sup> When administered after meals, an absorbed PPI will not be effectively activated because food-induced acid secretion and the highly acidic environment in the secretory canaliculi are nearly terminated when the plasma concentration of the drug reaches a peak level at 2–3 h after administration. Mainly based on data obtained from esomeprazole trials in western countries, PPIs are recommended to be administered 30 min before meals.<sup>(26–28)</sup>

On the other hand, the acid inhibitory effect of rabeprazole was shown to be not significantly influenced by timing of administration. In the present study, intra-gastric acidity after a single post-prandial oral dose of rabeprazole (10 mg) or esomeprazole (20 mg) was similarly raised and remained nearly identical for 24 h. On the other hand, the acid inhibitory effect of the latter was slightly stronger than that of the former when each was admin-



**Fig. 6.** Median intra-gastric pH during 24-h period after single post-prandial oral administration of 10 mg of rabeprazole (black lines) or 20 mg of esomeprazole (gray lines) in (a) rapid metabolizers ( $n = 5$ ), (b) intermediate metabolizers ( $n = 17$ ), and (c) poor metabolizers ( $n = 5$ ) of CYP2C19. At only 1 time point measurement in poor metabolizers, rabeprazole raised intra-gastric pH to a significantly higher level than esomeprazole, while there were no significant differences found for the other time points. \* $p < 0.05$ , statistically significant.

istered before meals, though the difference was not statistically significant. These results confirm a previous report showing that esomeprazole had a stronger acid inhibitory effect when administered 30 min before meals.

In the present study, direct comparisons of the acid inhibitory effects of the tested PPIs between pre- and post-prandial administrations was difficult, since the foods taken during the monitoring periods were not identical. However, when we compared the pre- and post-prandial administrations, esomeprazole was stronger with pre-prandial administration, as previously reported, while rabeprazole was equally potent irrespective of the timing of administration.

In Japan, approximately 80% of physicians instruct their patients to take PPIs after breakfast and approximately 10% after dinner.<sup>(29)</sup> Therefore, 90% of the patients take PPIs after meals. In such an environment, the acid inhibitory effects of the present PPI administrations are considered to be nearly identical, though esomeprazole may show a statistically non-significant benefit when administered before meals.

There are some limitations to our study. The first is lack of baseline intra-gastric pH data obtained without any drug administration. To more sensitively check the potency of any acid inhibitory effect, baseline pH data are necessary. Therefore, a comparison of the intra-gastric pH observed after rabeprazole and esomeprazole administrations is the only one possible in this study. Secondly, we did not measure the plasma PPI levels in subjects. Therefore, we could not correlate the pharmacokinetic disposition of PPI with the intragastric pH. The influence of meal on the absorption of PPIs and their acid inhibitory effects could not be made clear. Another is the lack of pH data during chronic administration of the PPIs, since these drugs are frequently used for chronic treatment. An additional study with chronic administrations of PPIs as well as baseline data may be necessary in the future.

In summary, we found that the intra-gastric pH values for 24 h after a single oral dose of rabeprazole (10 mg) or esomeprazole (20 mg) were nearly identical, especially when administered after meals. On the other hand, preprandial administration of esomeprazole may slightly augment its acid inhibitory effect.

## Conflicts of Interest

Furuta K received research grant from AstraZeneca KK, Eisai Co., Ltd. and Daiichi-Sankyo Co., Ltd. Fujiwara Y received lecture fee from Eisai Co., Ltd. The Center for Clinical Research and the First Department of Medicine at Hamamatsu University School of Medicine have received grants from Takeda Pharmaceutical Co., Ltd., AstraZeneca KK, Eisai Co., Ltd., Daiichi-Sankyo Co., Ltd., and Sugimoto M and Furuta T have received lecture fees from Takeda Pharmaceutical Co., Ltd., AstraZeneca KK, Eisai Co., Ltd., Daiichi-Sankyo Co., Ltd. Kusano M received lecture fee and research grant from Eisai Co., Ltd., and lecture fee from AstraZeneca KK and Daiichi-Sankyo Co., Ltd. Kato M received lecture fees from Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., and AstraZeneca KK and received research funds from Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., AstraZeneca KK, Astellas Pharmaceutical Co., Ltd., and Daiichi-Sankyo Co., Ltd. Iwakiri K received lecture fee from Eisai Co., Ltd. Higuchi H and Fujimoto K received research grant and lecture fees from AstraZeneca KK, Eisai Co., Ltd., Daiichi-Sankyo Co., Ltd. Naora K received research grants from AstraZeneca KK, Eisai Co., Ltd., and Takeda Pharmaceutical Co., Ltd. Arakawa T received research grant from Eisai Co., Ltd. and Otsuka Pharm Co., and lecture fee from Eisai Co., Ltd. Kinoshita Y received research grants and lecture fees from AstraZeneca KK, Eisai Co., Ltd., Daiichi-Sankyo Co., Ltd.

This study was funded by Eisai Co., Ltd.

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