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PHARMACOKINETICS AND DISPOSITION

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# Comparison of the kinetic disposition of and serum gastrin change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism

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**Abstract** *Background*: Little is known about differences in the disposition kinetics and pharmacological effects on gastrin levels between lansoprazole and rabeprazole given in a repeated dosing scheme with respect to the polymorphic *CYP2C19*.
*Aim*: To provide preliminary information that should be considered when prescribing proton-pump inhibitors (PPIs) for the treatment of acid-related diseases with reference to the *CYP2C19* genotypic status.
*Methods*: *Helicobacter pylori*-negative healthy volunteers were divided into the following three groups ($n = 5$ each) on the basis of genotyping for *CYP2C19*: homozygous (hmEMs) and heterozygous extensive metabolizers (htEMs), and poor metabolizers (PMs). All received once-daily 30-mg doses of lansoprazole or 10-mg doses of rabeprazole during an 8-day course in a crossover manner.
*Results*: The relative values for the area under the serum concentration–time curve (AUC) of lansoprazole and rabeprazole in the hmEMs, htEMs, and PMs after the final doses were 1:1.7:3.9 and 1:1.7:3.8, respectively. The relative AUCs of gastrin in the hmEMs, htEMs, and PMs were 1.6:2.6:3.1 for lansoprazole and 1.6:2.6:2.9 for rabeprazole, respectively.
*Conclusion*: The disposition kinetic behavior of the two PPIs is co-segregated with CYP2C19. The magnitude of CYP2C19-dependent drug availability in the systemic circulation and resulting gastrin response appears to be fairly similar between the two drugs within the same *CYP2C19* genotypic groups after a multiple-dosing regimen.

**Keywords** Pharmacokinetics · Pharmacodynamics · Proton pump inhibitors

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## Introduction

Lansoprazole and rabeprazole, benzimidazole derivatives (Fig. 1), are proton-pump inhibitors (PPIs) that act on the membrane $H^+/K^+$-ATPase in gastric parietal cells. These drugs are being increasingly used in the treatment of gastric and duodenal ulcer, gastroesophageal reflux disease, and other related hyperacidic conditions. Lansoprazole is metabolized extensively by the liver, and its primary metabolites in serum are 5-hydroxylansoprazole and lansoprazole sulfone (Fig. 1) [1, 2, 3]. Lansoprazole is analogous in its chemical structure and metabolic pathways to omeprazole [1, 2]. Previous in vitro human liver microsomal and in vivo human pharmacology studies have shown that the hydroxylation pathway of lansoprazole is mediated via polymorphic cytochrome $P_{450}$ (CYP) 2C19 [1, 2, 3, 4, 5]. In individuals with a poor metabolizer (PM) phenotype of CYP2C19, the area under the concentration–time curve (AUC) of lansoprazole is markedly increased [5]. Therefore, its pharmacodynamic effects are assumed to differ between patients with the two major metabolic statuses of CYP2C19 [e.g., extensive metabolizers (EMs) and PMs]. Recently, Adachi et al. [6] reported that median intragastric pH in the CYP2C19-related PMs during a 7-day lansoprazole dosing was higher than in the EMs. Furuta et al. [7] also reported that the pharmacological effect of omeprazole on inhibiting acid secretion in individuals with the PM genotype status of

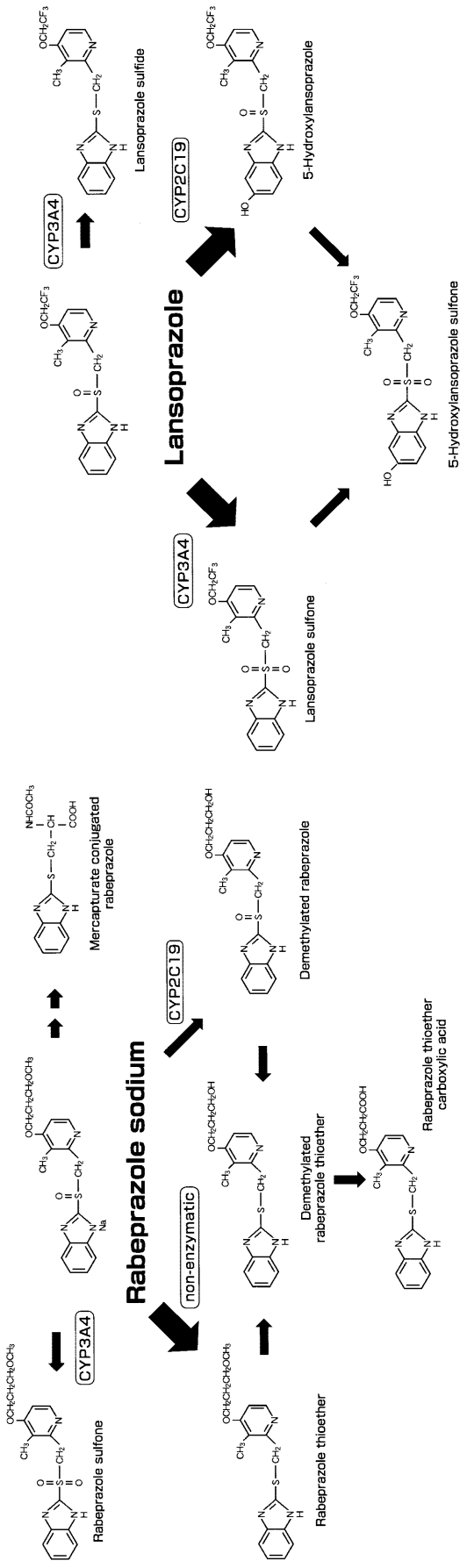


**Fig. 1** Metabolic pathways of lansoprazole [1, 2, 3] and rabeprazole [8, 9, 10], and the cytochrome $P_{450}$ (CYP) isoforms involved. The thickness of *arrows* indicates an approximate contribution of CYP isoforms to each of the metabolic pathways [1, 10]

*CYP2C19* was more strongly enhanced than in those with the EM genotype status. Higher serum drug concentrations attained in the PM subjects were assumed to account for the enhanced pharmacodynamic outcome achieved in them [7].

Although, like lansoprazole or omeprazole, rabeprazole is a substituted benzimidazole, the metabolic profile of rabeprazole differs somewhat from other PPIs, i.e., rabeprazole is metabolized mainly via a non-enzymatic reduction to rabeprazole thioether [8, 9, 10], and CYP2C19 and CYP3A4 are partly involved in the metabolism of rabeprazole (Fig. 1) [8, 9, 10]. Because rabeprazole has shown a lesser contribution of CYP2C19 to the overall metabolism than omeprazole [8, 9] or lansoprazole [10], the pharmacokinetics and pharmacodynamics of rabeprazole would be theoretically expected to be less affected by the CYP2C19-dependent pharmacogenetic differences. However, little is known about differences in the disposition kinetics and pharmacological effect on gastrin levels between lansoprazole and rabeprazole given in a repeated-dosing scheme with respect to the polymorphic CYP2C19. Gastrin is secreted from G cells in the antrum of the stomach [11], and disease states associated with achlorhydria or hypochlorhydria [12] and an inhibition of gastric acid secretion by omeprazole [7, 13] are known to stimulate gastrin release from G cells. Based on the background knowledge, as mentioned above, we intended to investigate the metabolic disposition characteristics of each PPI and serum gastrin levels after the single and 8-day repeated dosings of lansoprazole or rabeprazole in the different *CYP2C9* genotype groups. Therefore, the aim of the present study was to provide preliminary information that should be considered when prescribing PPIs (i.e., lansoprazole versus rabeprazole) administered in a multiple dosing therapy to patients with acid-related diseases with reference to the *CYP2C19*-related genotypic status.

## Methods

### Subjects and *CYP2C19* genotyping

Fifteen unrelated healthy subjects (5 women and 10 men) who were negative for *Helicobacter pylori* infection were enrolled in the current panel study. They ranged in age from 20 years to 26 years and in weight from 42 kg to 77 kg. None had taken any drugs for at least 1 week before and during the study. Each subject was physically normal and had no antecedent history of significant medical illness or hypersensitivity to any drugs. Their health status was judged to be normal on the basis of a physical examination with screening of blood chemistries, a complete blood count and urinalysis, and an electrocardiogram before the study. The study protocol was approved by the ethics review board of Tottori

University Hospital, and each subject gave her/his written informed consent before the study.

Genomic DNA was prepared from blood samples using the Toyobo blood kit on a Toyobo HMX-2000 robot (Toyobo, Osaka, Japan). The genotype of *CYP2C19* was identified using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis as previously described [14]. Subjects were genotypically classified into the following three groups on the basis of PCR-RFLP analysis for *CYP2C19* [14]: homozygous (*CYP2C19*1/*1*) EM group (hmEMs, $n = 5$), heterozygous (*CYP2C19*1/*3*) EM group (htEMs, $n = 5$), and PM (*CYP2C19*2/*2*, **2/*3*, **3/*3*) group ($n = 5$).

### Study protocol

Each subject received once-daily 30-mg doses of lansoprazole (Takepron, Takeda Chemical Industries, Osaka, Japan) or 10-mg doses of rabeprazole (Pariet, Eisai Co., Ltd., Tokyo, Japan) as the respective enteric-coated formulation with 150 ml water for 8 days in a randomized crossover manner, with a 2-week washout period between the two study phases. The pharmacokinetic disposition and gastrin measurement were assessed on the first and eighth postdose days (day 1 and day 8), and the participants came to the study site after an overnight fast on day 1 and day 8. During the first and final dosings, a lunch was served 4 h after the drug ingestion. Venous blood samples for the determination of serum concentrations of the parent drugs and their metabolites and gastrin were collected immediately before and 1, 2, 3, 4, 5, 7, 10, and 24 h after the first and final doses of lansoprazole or rabeprazole. In order to obtain the basal gastrin AUC values, gastrin concentrations were measured using the same sampling schedule within 2 days prior to the first administration. After the collection, blood samples were immediately centrifuged at 3000 rpm for 10 min, and the serum samples were separated. To determine serum concentrations of rabeprazole and its metabolite (i.e., rabeprazole thioether), 100 μl of a 1% diethylamine solution was added to the serum samples. All samples were stored at –30°C until assayed.

### Determinations of *H. pylori* and serum gastrin

Subjects were initially screened for *H. pylori* infection, which was determined on the basis of the [13C] urea breath test and a serologic test according to the respective methods previously described [15, 16]. When any one of these tests gave a positive result, an existing infection of *H. pylori* was diagnosed. Serum gastrin levels were measured using radioimmunoassay (Gastrin-RIA kit II, Dainabott Co., Ltd., Tokyo, Japan) at the laboratory center (Japan Clinical Laboratories, Osaka, Japan).

### Analytical techniques

The serum concentrations of lansoprazole and two primary metabolites, 5-hydroxylansoprazole and lansoprazole sulfone, were determined using high-performance liquid chromatography (HPLC) as described by Aoki et al. [17]. The lower detection limits, defined as the lowest concentration with a signal-to-noise ratio of 3, were at least 5 ng/ml for the analytes. The concentrations of rabeprazole and its main metabolite in serum, rabeprazole thioether, were also measured using an HPLC method [18] that was used for the pharmacokinetic study by Yasuda et al. [8] and the pharmacokinetic–pharmacodynamic study by Horai et al. [19]. The lower detection limits were 10 ng/ml for rabeprazole and 15 ng/ml for rabeprazole thioether. Recoveries of all analytes were greater than 80%, and the intra- and interassay coefficients of variation were less than 2% and less than 4%, respectively.

### Pharmacokinetic analysis

Pharmacokinetic analysis was performed in a model-independent manner, and non-compartmental kinetic parameters were calculated using the standard methods [20]. The postdose values for AUC from zero to 24 h for the parent drugs and their metabolites and gastrin in serum were calculated using the trapezoidal rule ($AUC_{0-24}$). The elimination rate constant ($k_e$) was estimated using the least regression analysis from the terminal post-distribution phase of the serum concentration–time curve. The AUC from zero hour to infinity ($AUC\infty$) was calculated as follows: $AUC\infty = AUC_{0-24} + Ct/k_e$, in which Ct represents the last measured time point serum concentration. The apparent oral clearance (CLo) was estimated according to the formula $CLo = Dose/AUC\infty$.

### Statistical analysis

The data are given as mean values (±SEM) throughout the text. One-way analysis of variance (ANOVA) combined with the least significant method (LSD) was used to compare means among the three groups. The statistical differences in the kinetic parameters and serum gastrin concentrations between the first (day 1) and final (day 8) doses were evaluated using a paired *t*-test. A $P$ value of less than 0.05 was considered to be statistically significant.

## Results

The mean kinetic parameters of lansoprazole and its primary metabolites, 5-hydroxylansoprazole and lansoprazole sulfone, in the three genotyping groups after the first (day 1) and final doses (day 8) are summarized in Table 1. There were significant ($P < 0.05$–$0.001$) differences between hmEMs and PMs in the kinetic parameters of lansoprazole, except for time to reach maximum concentration ($t_{max}$). The relative AUC ratio values of lansoprazole in hmEMs, htEMs, and PMs after the first and final doses were 1:1.8:5.6 and 1:1.7:3.9, respectively. In contrast, the CLo ratio values were 1:0.7:0.3 and 1:0.6:0.3, respectively. The mean AUC of lansoprazole after the final dose in PMs was smaller, with a significant difference ($P < 0.05$), than that after the first dose. Although the difference did not reach the significant level, a similar trend in the difference between the first and final postdose AUCs was observed in hmEMs and htEMs. The mean pharmacokinetic values for lansoprazole sulfone showed differences among the three groups that were similar to the differences observed with lansoprazole. In contrast, the pharmacokinetic data for 5-hydroxylansoprazole were opposite to that observed for lansoprazole and lansoprazole sulfone. The mean AUC values were significantly ($P < 0.05$) smaller in PMs than in hmEMs: the relative ratios of AUC in hmEMs, htEMs, and PMs after the first and final doses were 1:0.8:0.5 and 1:0.9:0.3, respectively, implying that the CYP2C19-mediated hydroxylation of lansoprazole to 5-hydroxylansoprazole was impaired in PMs. On postdose day 8, the mean AUC values of 5-hydroxylansoprazole tended to be smaller than those after the first dose in the three genotype groups (Table 1).

The mean kinetic data of rabeprazole and rabeprazole thioether in relation to the three genotype groups are summarized in Table 2. An intergenotypic difference was observed in various kinetic parameters: the mean AUC values of rabeprazole in PMs (1.31 ± 0.10 μg/ml/kg on day 1 and 1.48 ± 0.18 μg/ml/kg on day 8) were 3.3- and 3.8-fold greater than those in hmEMs

**Table 1** Pharmacokinetic data of lansoprazole and its two principal metabolites in the three different CYP2C19 genotypic groups. Values are presented as the mean (±SEM). $C_{max}$ maximum serum concentration, $t_{max}$ time to reach $C_{max}$, $t_{1/2}$ elimination half-life, *CLo* apparent oral clearance, *AUCm/AUCp* ratio of the area under the serum concentration–time curve of the metabolite to that of the parent drug lansoprazole from 0 h to infinity, *hmEMs* homozygous extensive metabolizers, *htEMs* heterozygous extensive metabolizers, *PMs* poor metabolizers

| | 1st day | | | 8th day | | |
|---|---|---|---|---|---|---|
| | hmEMs | htEMs | PMs | hmEMs | htEMs | PMs |
| Lansoprazole | | | | | | |
| $C_{max}$ (μg/ml) | 0.9 ± 0.2 | 1.1 ± 0.1* | 1.8 ± 0.3** | 0.7 ± 0.1 | 0.9 ± 0.1 | 1.4 ± 0.4 |
| $t_{max}$ (h) | 1.2 ± 0.2 | 1.8 ± 0.4 | 2.8 ± 0.6 | 1.6 ± 0.2 | 2.0 ± 0.3 | 1.2 ± 0.2 |
| $t_{1/2}$ (h) | 1.5 ± 0.2 | 1.3 ± 0.1 | 3.4 ± 0.3***, ### | 1.2 ± 0.1 | 1.5 ± 0.2 | 3.9 ± 0.2***, ### |
| AUC∞ (μg/ml/h) | 2.0 ± 0.3 | 3.6 ± 0.9 | 11.1 ± 1.9***, ## | 1.7 ± 0.3 | 2.9 ± 0.4 | 6.6 ± 0.9***, ## |
| CLo (l/kg/h) | 0.27 ± 0.05 | 0.19 ± 0.03 | 0.08 ± 0.04* | 0.32 ± 0.04 | 0.20 ± 0.03* | 0.10 ± 0.03** |
| 5-Hydroxylansoprazole | | | | | | |
| $C_{max}$ (μg/ml) | 0.08 ± 0.01 | 0.06 ± 0.004 | 0.03 ± 0.004***, # | 0.05 ± 0.007 | 0.06 ± 0.006 | 0.01 ± 0.003***, ### |
| $t_{max}$ (h) | 1.2 ± 0.2 | 1.8 ± 0.2 | 1.6 ± 0.2 | 1.2 ± 0.2 | 1.8 ± 0.2 | 1.8 ± 0.2 |
| $t_{1/2}$ (h) | 1.6 ± 0.3 | 1.7 ± 0.2 | 4.0 ± 0.7*, # | 1.2 ± 0.2 | 1.7 ± 0.2 | 3.2 ± 0.7**, # |
| $AUC_{\infty}$ (μg/ml/h) | 0.26 ± 0.04 | 0.22 ± 0.02 | 0.13 ± 0.02* | 0.15 ± 0.03 | 0.14 ± 0.03 | 0.04 ± 0.01* |
| AUCm/AUCp | 0.14 ± 0.02 | 0.08 ± 0.02* | 0.02 ± 0.002***, # | 0.09 ± 0.01 | 0.06 ± 0.02 | 0.01 ± 0.001***, # |
| Lansoprazole sulfone | | | | | | |
| $C_{max}$ (μg/ml) | 0.1 ± 0.02 | 0.2 ± 0.06 | 0.5 ± 0.06***, ## | 0.1 ± 0.01 | 0.1 ± 0.01 | 0.5 ± 0.06***, ### |
| $t_{max}$ (h) | 1.0 ± 0.01 | 1.8 ± 0.2 | 3.8 ± 0.8**, # | 1.2 ± 0.2 | 1.2 ± 0.2 | 3.4 ± 0.4***, ### |
| $t_{1/2}$ (h) | 6.1 ± 1.3 | 9.6 ± 2.0 | 9.7 ± 1.1 | 6.7 ± 0.9 | 5.9 ± 0.3 | 7.9 ± 0.4 |
| $AUC_{\infty}$ (μg/ml/h) | 1.18 ± 0.24 | 2.00 ± 0.17 | 7.78 ± 0.97***, ### | 1.09 ± 0.12 | 1.33 ± 0.11 | 6.11 ± 0.62***, ### |
| AUCm/AUCp | 0.62 ± 0.15 | 0.70 ± 0.20 | 0.82 ± 0.14 | 0.77 ± 0.17 | 0.53 ± 0.11 | 0.95 ± 0.08 |

*$P < 0.05$, **$P < 0.005$, and ***$P < 0.001$ compared with the hmEM group
#$P < 0.05$, ##$P < 0.005$, and ###$P < 0.001$ compared with the htEM group

(0.40 ± 0.14 μg/ml/kg and 0.39 ± 0.09 μg/ml/kg) after the first and final doses, respectively, and differed significantly ($P < 0.001$) between the two groups. The relative AUC values of rabeprazole in hmEMs, htEMs, and PMs after the first and final doses were 1:1.5:3.3 and 1:1.7:3.8, respectively. The mean AUC values of rabeprazole thioether in PMs (1.02 ± 0.26 μg/ml/kg and 0.72 ± 0.12 μg/ml/kg) were also significantly greater than those in hmEMs (0.22 ± 0.04 μg/ml/kg and 0.29 ± 0.06 μg/ml/kg) after the first and final doses, respectively. The relative ratios of AUC in hmEMs, htEMs, and PMs after the first and final doses were 1:3.8:4.6 and 1:2.6:2.5, respectively.

Before drug administration, there were no significant differences in the mean predose baseline AUCs of serum gastrin among the three genotype groups (Table 3). However, an intergenotypic difference in the AUC was observed after the first dose of lansoprazole or rabep-

**Table 2** Pharmacokinetic data of rabeprazole and rabeprazole thioether for the three different CYP2C19 genotypic groups. Values are presented as the mean (±SEM). $C_{max}$ maximum serum concentration, $t_{max}$ time to reach $C_{max}$, $t_{1/2}$ elimination half-life, *CLo* apparent oral clearance, *AUCm/AUCp* ratio of the area under the serum concentration–time curve of the metabolite to that of the parent drug lansoprazole from 0 h to infinity, *hmEMs* homozygous extensive metabolizers, *htEMs* heterozygous extensive metabolizers, *PMs* poor metabolizers

| | 1st day | | | 8th day | | |
|---|---|---|---|---|---|---|
| | hmEMs | htEMs | PMs | hmEMs | htEMs | PMs |
| Rabeprazole | | | | | | |
| $C_{max}$ (μg/ml) | 0.2 ± 0.1 | 0.4 ± 0.1 | 0.4 ± 0.1 | 0.2 ± 0.1 | 0.3 ± 0.1 | 0.5 ± 0.1 |
| $t_{max}$ (h) | 3.0 ± 0.3 | 2.8 ± 0.4 | 3.8 ± 0.5 | 3.2 ± 0.2 | 3.0 ± 0.4 | 2.8 ± 0.5 |
| $t_{1/2}$ (h) | 0.6 ± 0.1 | 1.1 ± 0.1 | 2.3 ± 0.4***, # | 0.9 ± 0.3 | 1.4 ± 0.3 | 2.1 ± 0.1* |
| AUC∞ (μg/ml/h) | 0.40 ± 0.14 | 0.61 ± 0.09 | 1.31 ± 0.10***, ## | 0.39 ± 0.09 | 0.65 ± 0.17 | 1.48 ± 0.18***, # |
| CLo (l/kg/h) | 0.63 ± 0.18 | 0.35 ± 0.05 | 0.15 ± 0.02* | 0.49 ± 0.09 | 0.42 ± 0.10 | 0.13 ± 0.01* |
| Rabeprazole thioether | | | | | | |
| $C_{max}$ (μg/ml) | 0.05 ± 0.01 | 0.09 ± 0.01 | 0.10 ± 0.02 | 0.07 ± 0.02 | 0.09 ± 0.02 | 0.09 ± 0.01 |
| $t_{max}$ (h) | 3.2 ± 0.2 | 3.4 ± 0.5 | 6.4 ± 1.2*, # | 3.6 ± 0.2 | 4.2 ± 0.7 | 3.8 ± 0.5 |
| $t_{1/2}$ (h) | 2.7 ± 0.7 | 4.5 ± 1.1 | 5.5 ± 1.0 | 2.0 ± 0.2 | 5.1 ± 1.4 | 6.2 ± 1.0* |
| AUC∞ (μg/ml/h) | 0.22 ± 0.04 | 0.84 ± 0.19 | 1.02 ± 0.26* | 0.29 ± 0.06 | 0.75 ± 0.12* | 0.72 ± 0.12* |
| AUCm/AUCp | 0.70 ± 0.11 | 1.47 ± 0.53 | 0.85 ± 0.32 | 0.78 ± 0.11 | 1.45 ± 0.39 | 0.52 ± 0.09 |

*$P < 0.05$, **$P < 0.005$, and ***$P < 0.001$ compared with the hmEM group
#$P < 0.05$, ##$P < 0.005$, and ###$P < 0.001$ compared with the htEM group

**Table 3** Mean (±SEM) of the area under the gastrin concentration vs time curve (AUC) in the three genotype groups after single (first day) and multiple (eighth day) doses of lansoprazole or rabeprazole. *Ratio* the ratio of AUC on each day to baseline AUC, *hmEMs* homozygous extensive metabolizers, *htEMs* heterozygous extensive metabolizers, *PMs* poor metabolizers

| | AUC (pg/ml/h) | | |
|---|---|---|---|
| | hmEMs | htEMs | PMs |
| Baseline | 1037.1 ± 72.7 | 963.2 ± 95.0 | 1160.0 ± 87.9 |
| Lansoprazole | | | |
| 1st day | 1213.1 ± 118.5 | 1459.2 ± 329.5 | 1806.7 ± 324.7 |
| Ratio | 1.18 ± 0.11 | 1.54 ± 0.30 | 1.60 ± 0.37 |
| 8th day | 1616.7 ± 258.2 | 2383.6 ± 544.5 | 3576.4 ± 581.4* |
| Ratio | 1.58 ± 0.25 | 2.60 ± 0.71 | 3.12 ± 0.63 |
| Rabeprazole | | | |
| 1st day | 1019.4 ± 110.4 | 1341.1 ± 240.4 | 1799.4 ± 152.0 |
| Ratio | 1.01 ± 0.13 | 1.41 ± 0.21 | 1.56 ± 0.13 |
| 8th day | 1601.5 ± 175.1 | 2518.5 ± 472.4 | 3205.1 ± 454.4* |
| Ratio | 1.55 ± 0.15 | 2.61 ± 0.67 | 2.86 ± 0.70 |

*$P < 0.05$ compared with the hmEM group

razole. After the final dose of lansoprazole or rabeprazole, the AUCs of serum gastrin differed significantly ($P < 0.05$) between hmEMs and PMs, and the relative ratios (AUC in the final dose/basal AUC) of lansoprazole and rabeprazole were 1.6:2.6:3.1 and 1.6:2.6:2.9, respectively, in hmEMs:htEMs:PMs. The mean serum gastrin AUC values in htEMs observed during both the lansoprazole and rabeprazole trial phases were intermediate between those in hmEMs and PMs (Table 3).

## Discussion

PPIs have dramatically influenced the management of hyperacidic-related peptic disorders over the last 10 years. Four of these agents, omeprazole, lansoprazole, pantoprazole, and rabeprazole, are now available in some countries. Several comparative studies [21, 22, 23, 24, 25, 26] of the pharmacokinetics, potency, acid suppression, clinical efficacy, and toxicity have been performed previously and have addressed the appropriate use of PPIs in the treatment of acid-related diseases. Unfortunately, none of these clinical studies [21, 22, 23, 24, 25, 26] have taken into account the genetic polymorphism of CYP2C19, a major enzyme for the metabolism of PPIs in the liver [1, 2, 10]. Therefore, we were prompted to assess whether the kinetic and dynamic profiles would differ between lansoprazole and rabeprazole in light of the genetically determined CYP2C19 polymorphism. However, because both lansoprazole and rabeprazole are sulfoxidated via CYP3A4 [1, 2, 3, 8, 9, 10] (Fig. 1), one may raise a question why we did not determine CYP3A4 phenotyping and/or genotyping for our study subjects. Indeed, several recent studies have reported that CYP3A4 allelic variants exist in Caucasian and African-American populations [27, 28, 29, 30, 31, 32, 33, 34, 35, 36]. However, whether these isoform variants would be associated with an altered metabolism of the relevant substrate drugs appears to be controversial and conflicting [32, 33, 34, 35, 36]. Because the existence of CYP3A4-related PMs has not been reported in any Japanese population, we did not take into account CYP3A4-related phenotyping/genotyping factor(s) in the present study. Nevertheless, the combined pharmacogenetic assessments (CYP2C19 and 3A4) would be required for future studies assessing whether *CYP2C19* genotyping alone would be a useful clinical tool for optimizing a PPI-based therapy. With this limitation in mind, we wish to discuss our findings as below.

Our results showed that the metabolism of lansoprazole and rabeprazole cosegregates with CYP2C19, and the dynamic effect of these drugs on serum gastrin concentrations depends significantly on the CYP2C19 polymorphism characterized by the greater AUC values of either of the drugs and by the greater postdose gastrin concentrations (or AUCs) in PMs than those in hmEMs and htEMs. However, the magnitude of the CYP2C19-mediated metabolism plus the pharmacodynamic effect on serum gastrin concentrations does not appear to differ between the two drugs under the repeated-dose condition within the same genotypic groups, while the pharmacokinetic and pharmacodynamic effects of the two drugs did significantly differ among the three different genotypic groups.

Adachi et al. [6] recently conducted a comparative study to evaluate the effect of *CYP2C19* genotype status on intragastric pH during a 7-day dosing scheme with lansoprazole versus rabeprazole. They demonstrated that the median pH on the last day of the 7-day treatment with rabeprazole was not influenced by the *CYP2C19* genotype patterns, whereas the median pH in PMs after the last day of the 7-day treatment with lansoprazole was higher than in htEMs and hmEMs. However, because Adachi et al. [6] did not measure lansoprazole or rabeprazole concentrations, it remains obscure whether the drug concentration–intragastric pH relationship would exist and, if so, would differ among the hmEMs, htEMs, and PMs.

Because of the irreversible blockade of the therapeutic target by PPIs, no direct and simple relationship between the serum concentration–time profile of the drug and pharmacodynamic response has been reported. However, a clear relationship could be obtained by the use of the maximum effect ($E_{max}$) model for omeprazole [37, 38] and lansoprazole [39], in which serum concentrations were integrated over the postdose time

(e.g., AUC). According to the $E_{max}$ model, the mean half-maximal effective AUC value ($EAUC_{50}$) of lansoprazole was 899 ng/ml/h [39]. Thus, maximal acid suppression may be obtainable with oral doses resulting in an AUC value of approximately 2 μg/ml/h. As shown in Table 1, mean AUC values in htEMs and hmEMs on the last dosing day were lower than and close to, respectively, this threshold. This appears to be the most likely reason for explaining the differences in intragastric pH after a 7-day course of lansoprazole dosing between EMs and PMs of CYP2C19 observed by Adachi et al. [6]. Unfortunately, the correlation between pharmacokinetics and pharmacodynamic outcome for rabeprazole has, to our knowledge, not been well documented. However, the present study coupled with the findings of Adachi et al. [6] suggests a low $EAUC_{50}$ for rabeprazole. Taken together, not only the *CYP2C19* genotype status but also the AUC value of the PPIs would be important determinants with regard to their pharmacodynamic effects (e.g., gastric pH, serum gastrin). Thus, this consideration appears to be clinically important when prescribing either of PPIs for the treatment of acid-related diseases.

Although the intragastric pH is the best or most direct pharmacological index in the treatment of acid-related disorders when using PPIs, its application in routine clinical settings is restricted because of its invasiveness and cost. However, the pharmacodynamic effects of PPIs can be evaluated using plasma or serum gastrin levels, because gastrin release from G cells is stimulated by an increase in intragastric pH [13]. When a PPI inhibits acid secretion, plasma or serum gastrin levels will be increased according to the degree of acid inhibition. Therefore, serum gastrin concentration was used as an indirect index or surrogate marker of the pharmacodynamic effect in the present study. Indeed, serum gastrin concentrations correlate well with gastric acid suppression, which has led to the use of the postdose resulting gastrin response as a surrogate marker for assessing a drug-induced antisecretory effect [40].

As shown in Table 3, the mean gastrin AUC differed among the three genotype groups, and thus an intergenotypic difference in gastric acid suppression would be assumed. These results are consistent with the findings by Furuta et al. [7], in which the relative ratio of gastrin AUC after a single dose of omeprazole was 1.1:1.2:1.5 in hmEMs:htEMs:PMs. They also demonstrated that the intergenotypic difference in serum gastrin AUC was synchronized with that in mean intragastric pH. However, the difference in mean intragastric pH among the three genotype groups (1:1.5:2.1) tended to be greater than that in gastrin AUC (1:0.9:1.5). Therefore, one might ask whether serum gastrin concentrations would accurately reflect the PPI-induced changes in intragastric pH. Although previous investigators indicated that serum gastrin concentrations returned to normal or baseline values shortly after the antisecretory treatment with rabeprazole or ranitidine was discontinued [41, 42], this phenomenon appears to be in conflict with the long-lasting action of PPIs [43]. The clinical significance of short-term postdose increases in circulating gastrin that we used as a surrogate marker in the study, compared with the gastric acid inhibition directly measured using a pH electrode, remains unclear at present.

An interesting observation on the difference in kinetic behavior between the two drugs seen in the present study was that the AUC values of lansoprazole decreased from the first to the final dose in all three genotype groups, whereas no such change was observed for rabeprazole. The reduction magnitude of the AUC was significantly greater for lansoprazole than for rabeprazole in PMs. Although it is highly difficult for us to interpret these findings, we wish to offer our explanation for them on an assumptive basis as follows: lansoprazole is known to primarily be metabolized by CYP2C19 and CYP3A4 to 5-hydroxylansoprazole and lansoprazole sulfone, respectively (Fig. 1) [1, 2, 3, 10]. As shown in Table 1, the mean AUC ratio of lansoprazole sulfone to lansoprazole in PMs on day 8 (0.95) increased by 16% from that on day 1 (0.85). In addition, the AUC of 5-hydroxylansoprazole tended to decrease on the repeated administration in all three genotype groups, suggesting the possibility that the formation of 5-hydroxylansoprazole from lansoprazole mediated by CYP2C19 might have occurred in a saturable fashion during the repetitive dosings. A likely reason for the decrease in serum lansoprazole AUC in PMs (from 11.1 μg/ml/h on day 1 to 6.6 μg/ml/h on day 8, Table 1) might be that CYP3A4 involved in the metabolism of lansoprazole to lansoprazole sulfone (Fig. 1) would play a somewhat more dominant role in PMs than in EMs. The most plausible reason that no discernible pharmacokinetic parameter changes in rabeprazole were observed (Table 2) would be that rabeprazole is metabolized mainly via a non-enzymatic reduction to the thioether metabolite, and CYP2C19 and 3A4 are only partly involved in the metabolism of rabeprazole (Fig. 1) [1, 2, 8, 9, 10]. Obviously, the assumptive explanations given above must require further studies for their clarifications.

In conclusion, our results show that the CYP2C19-mediated metabolism and the CYP2C19-related pharmacodynamic effect on serum gastrin concentrations did not appear to differ between the two PPIs, lansoprazole and rabeprazole, within the same genotyping groups under the repeated-dose condition. However, the pharmacokinetic and pharmacodynamic outcomes of the two drugs were significantly different among the three genotype groups. Therefore, the genetic polymorphism of CYP2C19 should be considered as a clinical determinant in the treatment of acid-related disorders with a PPI.

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