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PHARMACOGENETICS

Effect of *MDR1* C3435T polymorphism on lansoprazole in healthy Japanese subjects

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Abstract
Background and aims The effect of multidrug resistance transporter gene 1 (*MDR1*) on the bioavailability and kinetics of several substrates has not yet been fully elucidated. We evaluated the influence of *MDR1* C3435T polymorphism on the pharmacokinetics and pharmacodynamics of lansoprazole in Japanese subjects.
Methods Fifteen healthy volunteers with the rapid extensive metabolizer genotype of *CYP2C19* were classified into three *MDR1* C3435T genotype groups: C/C (n=5), C/T (n=5), and T/T (n=5). Lansoprazole 30 mg was administered orally for 15 days. The intragastric pH and plasma lansoprazole levels were determined on days 1 and 15.
Results On day 1, the mean C_{max} of lansoprazole in the T/T group was significantly higher than that in the C/C or C/T groups (T/T 1,248, C/C 618, C/T 607 ng/ml; P=0.038). On day 15, similar *MDR1* genotype-dependent differences were observed in the C_{max} of lansoprazole, although smaller than the differences observed on day 1. In contrast, the intragastric pH attained after lansoprazole administration did not differ among *MDR1* genotype groups on either day 1 or day 15.
Conclusion Although the sample size was small, our study demonstrated that the *MDR1* C3435T polymorphism influenced the pharmacokinetics, but not the pharmacodynamics (i.e., intragastric pH), of lansoprazole in rapid metabolizers of CYP2C19.

Keywords Lansoprazole · *MDR1* · Polymorphism · CYP2C19

Abbreviations

CYP2C19	Cytochrome P450 2C9
Helicobacter pylori	*H. pylori*
IM	Intermediate metabolizer
MDR1	Multidrug resistance transporter gene 1
PPI	Proton-pump inhibitor
PM	Poor metabolizer
RM	Rapid metabolizer

Introduction

Proton-pump inhibitors (PPIs) such as lansoprazole, omeprazole, rabeprazole, esomeprazole, and pantoprazole are in

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current clinical use as potent gastric-acid inhibitors. PPIs inhibit gastric-acid secretion by interaction with H^+/K^+-ATPase in gastric parietal cells [1, 2]. The major indication for PPIs is acid-related diseases, such as peptic ulcer, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome [3–7]. PPIs are also used to eradicate *Helicobacter pylori* (*H. pylori*) infection in combination with antimicrobial agents such as clarithromycin (CAM), metronidazole (MNZ), and amoxicillin (AMPC) [8–10].

PPIs are mainly metabolized in the liver by cytochrome P450 isoenzyme 2C19 (CYP2C19), an enzyme whose activity varies due to genetic differences. The genotypes of *CYP2C19* are classified into three groups: rapid metabolizer (RM=**1/*1*), intermediate metabolizer (IM=**1/*X*), and poor metabolizer (PM=**X/*X*, where **X*=**2* or **3*) [11]. The pharmacokinetics and pharmacodynamics of PPIs differ by *CYP2C19* genotype [12, 13]: during PPI treatment, plasma PPI and intragastric pH levels are lowest in the RM group and highest in the PM group. These genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs are reflected in the cure rates for *H. pylori* infection following a PPI-based treatment regimen [11, 14]. Factors other than *CYP2C19* polymorphism that affect the cure rates of *H. pylori* infection include bacterial susceptibility to clarithromycin [15], smoking, and compliance, among others. However, inter-individual differences in clinical outcomes are still observed even in individuals who exhibit similarities with regard to these factors, suggesting that other factors influence the pharmacokinetics and pharmacodynamics of PPIs.

MDR1 codes the P-glycoprotein (P-gp), a component of adenosine triphosphate (ATP)-binding-cassette (ABC) transporters [16]. P-gp functions as the energy-dependent exporter of substances from cells and prevents accumulation of potentially toxic and also carcinogenetic substances and metabolites in cells. P-gp expression represents one of the most important mechanisms for the failure of chemotherapeutic treatment of cancer [17]. P-gp is expressed on the surface of not only cancer cells but also normal cells such as hepatocytes, enterocytes, and endothelial cells of brain blood vessels. Genetic differences affect the expression of *MDR1* [18]. A synonymous single nucleotide polymorphism (SNP) in exon 26 (C3435T) has sometimes been reported to be associated with altered P-gp activity [18]. Plasma levels of digoxin, a representative substrate of *MDR1*, have been found to differ among *MDR1* C3435T genotype groups [19].

Lansoprazole is a substrate of P-gp [20], but the impact of *MDR1* C3435T polymorphism on the pharmacokinetics and pharmacodynamics of lansoprazole has not been fully elucidated. Recent clinical studies have revealed that lansoprazole-based therapies for *H. pylori* infection are affected by *MDR1* C3435T polymorphism [21, 22]). However, several reports have indicated that P-gp activity is also affected by the G2677A/T (Ala893Thr or Ala893Ser) and/or C1236T (synonymous) polymorphism [23, 24]. Interestingly, *MDR1* C3435T is in linkage disequilibrium with other polymorphisms such as G2677A/T and C1236T. Meta-analysis has suggested that these haplotypes, rather than the single polymorphism, may be more predictive of P-gp activity [25]. Here, we investigated whether *MDR1* C3435T polymorphism as well as haplotypes affected the pharmacokinetics and pharmacodynamics of lansoprazole in healthy Japanese subjects with the rapid metabolizer genotype of *CYP2C19*.

Methods

Eighty healthy Japanese subjects were invited to be genotyped for *CYP2C19* and *MDR1* C3435T and serologically tested for *H. pylori* infection as described below. Of these, 15 with the RM genotype of *CYP2C19* (**1/*1*) and different *MDR1* C3435T genotypes were enrolled into this study. All participants were seronegative for *H. pylori* infection and had different *MDR1* C3435T genotypes (*MDR1* 3435C/C=5, C/T=5, T/T=5), with no history of peptic ulcer, hepatic disorders, cardiovascular disorders, renal diseases, or other serious conditions. Participants had consumed no alcohol or taken any drugs for at least 1 month prior to this study.

Participants were given a single daily oral dose of 30 mg lansoprazole (Takepron, Takeda Pharmaceutical, Osaka, Japan) at 0800 for 15 days. Intragastric pH was monitored 24 h/day, and blood samples were collected at 0, 0.5, 1, 2, 3, 5, 7, 10, and 24 h after drug administration on days 1 and 15. Meals with the same contents were served at 0800, 1230, and 1800 on days 1 and 15, with caloric counts measuring 300, 600, and 800 kcal, respectively. All subjects gave written informed consent, and the study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine.

Genotyping of *CYP2C19* and *MDR1*

CYP2C19 genotyping was performed by PCR-RFLP using DNA extracted from whole blood [26]. Those subjects homozygous for the 1* allele (**1/*1*) were defined as RMs of *CYP2C19*.

MDR1 C3435T polymorphisms were identified by PCR-RFLP as reported previously [27] and classified as C/C, C/T, or T/T polymorphism. *MDR1* C1236T and G2677A/T genotypes were similarly determined in all subjects and classified as C/C, C/T, or T/T for C1236T, and as G/G, G/T, G/A, A/T, or T/T for G2677A/T [28].

Diagnosis of *H. pylori* infection

H. pylori infection was assessed by serological testing. Anti-*H. pylori* antibody titer was measured by enzyme immunoassay (E plate; Eiken Chemical, Tokyo, Japan) with an assay value <10 U/mL considered negative and >10 U/mL considered positive for infection [29].

Analysis of lansoprazole in plasma

Plasma concentrations of lansoprazole were determined by liquid chromatography (HPLC)/mass spectrometry (LC/MS). Briefly, plasma samples (0.2 mL) containing 10 ng of isobutyl p-hydroxybenzoate as an internal standard were diluted with 0.7 mL of water and applied to an OASIS HLB extraction cartridge (Waters, Milford, MA, USA). The cartridge was then washed with 5% methanol in water (1.0 mL) and eluted with ethanol (1.0 mL). The elution was evaporated under a stream of nitrogen gas at 40°C, and the residue was reconstituted in 200 μL of mobile phase (acetonitrile/10 mM ammonium acetate, 44:56, v/v). A 30-μL aliquot was injected into the HPLC apparatus and analyzed using an analytical column (Symmetry C_{18}, 5 mm, 2.1×150 mm; Waters) with the mobile phase delivered at a flow rate of 0.3 mL/min at 40°C. The mass spectrometer was operated in positive ionization mode with selected ion recording acquisition at 370 *m/z* for lansoprazole. The limit of quantification was 0.1 ng/mL, and the intra-assay coefficient of variation was <10.4%.

Statistical analysis

Numerical values are given as mean±SD. The pharmacokinetic parameters for lansoprazole were estimated by noncompartmental analysis. Maximum plasma concentration (C_{max}) and the time at maximum plasma concentration (T_{max}) were estimated directly from observed plasma concentration-time data. The area under the concentration vs. time curve (AUC) was calculated by the trapezoidal rule for the observed values. Genotype frequencies of *MDR1* C1236T, C3435T, and G2677A/T genotypes were compared using the χ^2-test. Statistically significant differences in pharmacokinetic and pharmacodynamics parameters among the three different *MDR1* C3435T genotype groups were assessed by one-way ANOVA followed by the Scheffe's multiple comparison test. Presence or absence of changes in pharmacological parameters between day 1 and 15 was assessed by paired *t*-test. All *P*-values were two-sided, and values were considered statistically significant at $P<0.05$.

Results

Examination of the demographic data of subjects found that mean age and sex did not differ significantly among the three *MDR1* genotype groups (Table 1). We observed a possible linkage disequilibrium between *MDR1* C3435T and G2677A/T polymorphisms. The incidence of the 2677 G/G genotype was markedly high in the 3435 C/C group, that of 2677 G/T was markedly high in the 3435 C/T group, and that of 2677 T/T was markedly high in the 3435 T/T group (Table 1). A similar but not statistically significant tendency was observed between C3435T polymorphism and C1236T polymorphism.

Figure 1 shows the mean plasma concentration-time curves of lansoprazole as a function of *MDR1* C3435T polymorphism on day 1 and day 15. Concentrations differed among the three different *MDR1* C3435T genotypes following a 30-mg single-dose administration of lansoprazole. Plasma lansoprazole levels in the T/T group appeared higher than those in the C/T and C/C groups on day 1 (Fig. 1a). This *MDR1* C3435T genotype-dependent difference in levels was still apparent on day 15, but appeared smaller than on day 1 (compare Fig. 1b with a).

Table 1 Demographic characteristics of study subjects as a function of *MDR1* C3435T genotype status

		C/C (*n*=5)	C/T (*n*=5)	T/T (*n*=5)	*P*-value
Age (years)		22.4±0.3	22.4±0.3	22.0±0.9	0.843[a]
Sex (m/f)		3/2	3/2	4/1	0.741[a]
Height (cm)		171.6±3.9	169.0±2.8	165.8±2.2	0.433[a]
Weight (kg)		60.4±3.4	61.2±3.5	58.8±2.4	0.862[a]
C1236T (*n*)	C/C	2	0	0	0.632[b]
	C/T	2	2	2	
	T/T	1	3	3	
G2677A/T (*n*)	G/G	4	0	0	0.001[b]
	G/A	1	0	0	
	G/T	0	4	1	
	A/T	0	1	0	
	T/T	0	0	4	

[a] *P*-value for one-way ANOVA

[b] *P*-value for χ^2-test

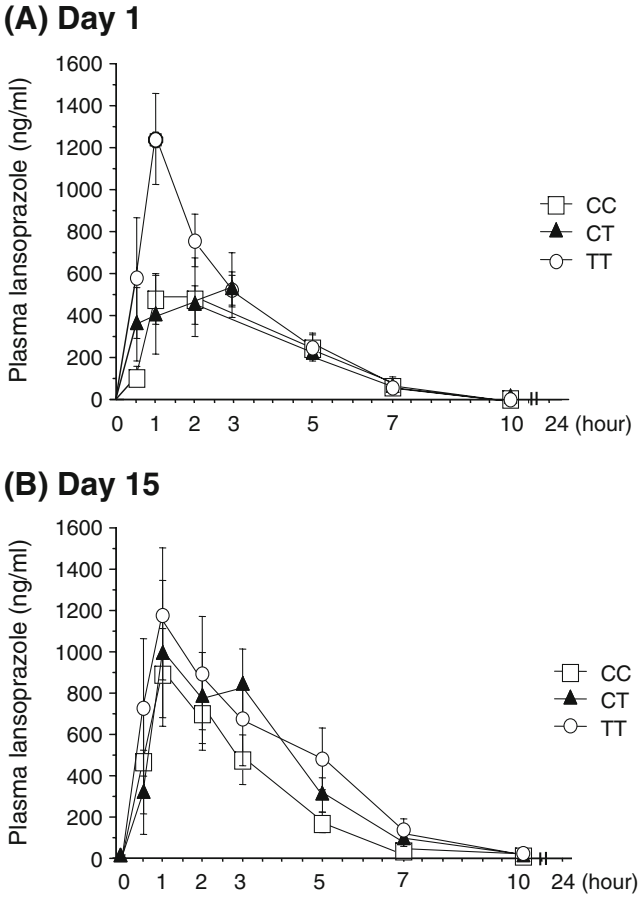

Fig. 1 Plasma lansoprazole level as a function of *MDR1* C3435T genotype status on day 1 (**a**) and day 15 (**b**). A 30-mg dose of lansoprazole was given in a single daily oral administration for 15 days. Blood samples were collected on days 1 and 15 at the indicated time points. The peak of the plasma lansoprazole concentration on day 1 was higher in the T/T group (*circles*) than in the other groups (*triangles* C/T and *squares* C/C) (**a**)

Pharmacokinetic parameters of lansoprazole are summarized in Table 2. On day 1, the mean C_{max} in the T/T group was significantly higher than that in the C/C and C/T groups (T/T 1,248 vs. C/C 618 and C/T 607 ng/ml; P=0.043, 0.042) (Table 2). Mean $AUC_{0–24\ h}$ on day 1 was highest in the T/T group (3,653 h·ng/ml), although the difference between groups was not statistically significant (C/C2,506, C/T2,375 h·ng/ml) (Table 2). Further, mean T_{max} on day 1 was shortest in the T/T group.

However, these *MDR1* C3435T genotype-dependent differences in pharmacokinetics parameters observed on day 1 seemed to lessen by day 15. The mean C_{max} of lansoprazole increased from day 1 to 15 in the C/C and C/T groups, and the increase in the C/T group was statistically significant (P=0.014) (Fig. 2). However, this increase was not observed in the T/T group, resulting in a smaller difference in C_{max} on day 15 among the three groups (mean C_{max} at day 15:C/C1,021, C/T 1,332, and T/T 1,459 ng/ml). Although mean C_{max} of the T/T group on day 15 still appeared highest of the three, the difference was not statistically significant.

Similarly, the mean $AUC_{0–24\ h}$ of the *MDR1* 3435 C/C, C/T, and T/T groups on day 15 were 2,901, 3,897, and 4,654 h·ng/ml, respectively, with no statistically significant differences among them. Further, T_{max} for all three groups on day 15 appeared nearly identical (Table 2).

Figures 3b and c show intragastric pH profiles of the different *MDR1* genotype groups over 24 h on days 1 and 15, respectively. Control profiles of intragastric pH are shown in Fig. 3a, and intragastric pH parameters are summarized in Table 3. The mean 24-h intragastric pH on day 1 was 3.1 in the C/C group, 3.5 in the C/T group, and 3.8 in the T/T group, with no statistically significant differences in the mean 24-h intragastric pH among the three genotypes (P=0.566). Similarly, there were no statistically significant differences among *MDR1* genotype group for the intragastric pH profile on day 15, nor was there a statistically significant difference in the percentage time for intragastric pH<4 among the groups on both days 1 and 15 (Table 3).

Influence of *MDR1* G2677A/T/C3435T haplotype

To further analyze the influence of *MDR1* haplotype, we compared the pharmacokinetics and pharmacodynamics of

Table 2 Pharmacokinetics of lansoprazole on days 1 and 15

		C/C (n=5)	C/T (n=5)	T/T (n=5)	P-value (one-way ANOVA)
Day 1	C_{max} (ng/ml)	618±375*	607±284*	1,248±494	0.038
	T_{max} (h)	2.6±1.5	1.9±1.1	1.0±0.2	0.088
	$AUC_{0–24\ h}$ (h·ng/ml)	2,506±1,260	2,375±686	3,653±1,314	0.183
Day 15	C_{max} (ng/ml)	1,021±360	1,332±525	1,459±646	0.423
	T_{max} (h)	1.5±1.0	1.8±1.1	2.7±2.2	0.453
	$AUC_{0–24\ h}$ (h·ng/ml)	2,901±1178	3,897±1052	4,654±1576	0.140

C_{max} Maximum concentration, T_{max} time to reach C_{max}, $AUC_{0–24\ h}$ area under the plasma concentration-curve from 0 to 24 h

*P<0.05 compared with subjects in the T/T group

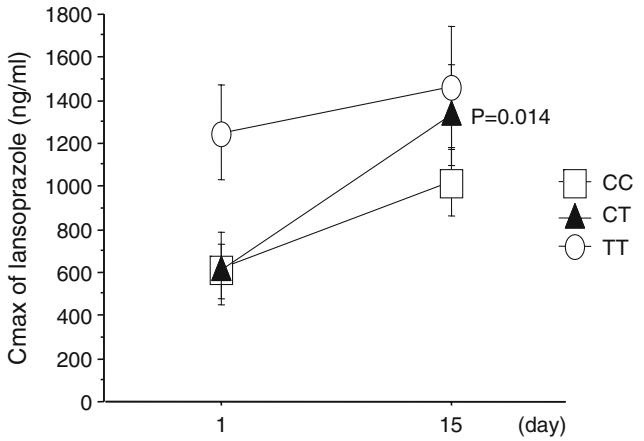

Fig. 2 Changes in C_{max} of lansoprazole from day 1 to day 15 as a function of *MDR1* C3435T genotype status. There was a statistically significant difference in the mean C_{max} of lansoprazole among the three different genotype groups on day 1. From day 1 to day 15, the means of C_{max} in the C/C (*squares*) and C/T (*triangles*) groups increased, and the increase in the C/T group in particular was statistically significant (P=0.014), while the increase in the T/T group (*circles*) was small. This resulted in a smaller apparent difference in the means of C_{max} among the three genotype groups on day 15 then on day 1

lansoprazole in the groups with the *MDR1* 2677G/G and 3435C/C (GC/GC) type and the *MDR1* 2677T/T and 3435T/T (TT/TT) type. The C_{max} and $AUC_{0-24\ h}$ of lansoprazole appeared higher, but not significantly so, in the TT/TT group in comparison with measurements in the GC/GC group on both day 1 and day 15. However, this haplotype demonstrated no influence on the mean 24-h intragastric pH attained by lansoprazole (Table 4).

Discussion

Here, we found that the pharmacokinetics of lansoprazole were influenced by the *MDR1* C3435T polymorphism in a group of Japanese subjects. However, the acid inhibition attained with daily administration of 30 mg of lansoprazole was not affected by this polymorphism. Further, these findings demonstrate for the first time that the influence of the *MDR1* C3435T genotypic difference on the pharmacokinetics of lansoprazole decreases following repeated dosing. We therefore assume that the *MDR1* C3435T polymorphism is of limited importance in the usual therapeutic dosing schedule for lansoprazole.

The multidrug-resistant transporter encoded by *MDR1* is a member of the ATP-binding cassette superfamily of membrane transporters [27] and has the potential to expel unnecessary or toxic exogenous substances or metabolites from cells. More than 40 SNPs have been discovered in *MDR1*. In 2000, Hoffmeyer et al. [19] first demonstrated that an SNP in exon 26 of the *MDR1* gene (C3435T) was

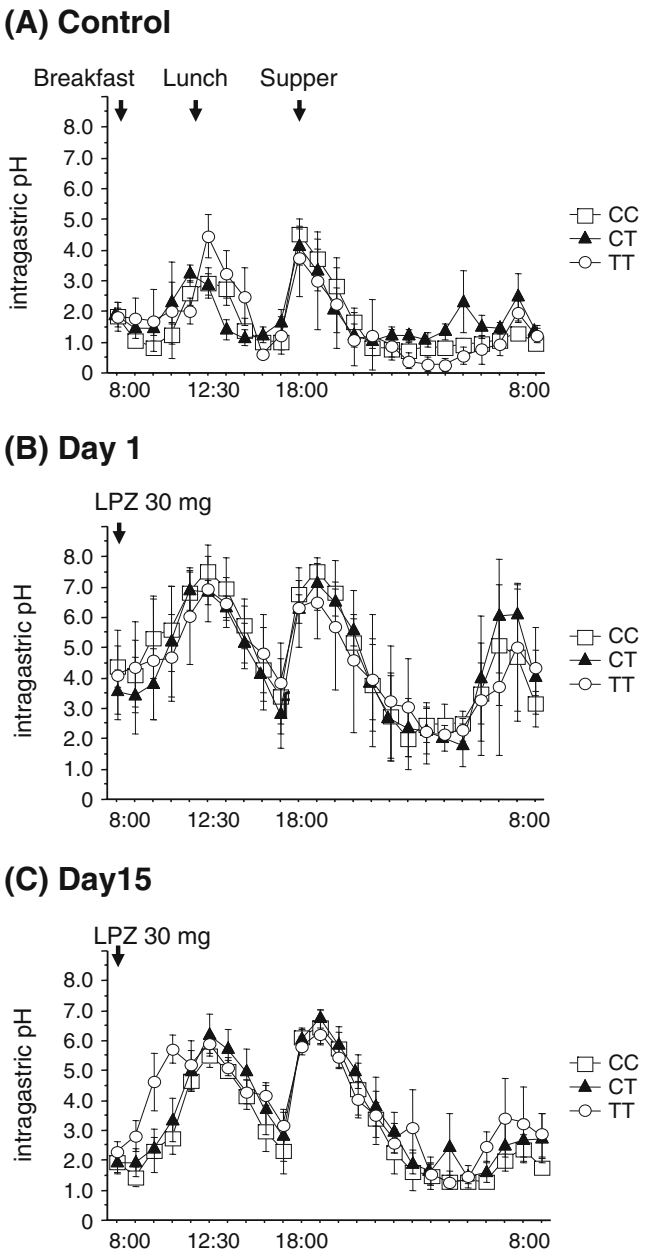

Fig. 3 The 24-h intragastric pH profiles as a function of *MDR1* C3435T genotype status. **a** Control intragastric pH profiles. **b** and **c** Intragastric pH levels with daily dosing of lansoprazole 30 mg on days 1 and 15, respectively. The intragastric pH profiles of the three *MDR1* C3435T genotype groups (*squares* C/C, *triangles* C/T, and *circles* T/T) appeared nearly identical, irrespective of dosing schedule

associated with lower intestinal *MDR1* levels and higher plasma levels of orally dosed digoxin. Thus, the *MDR1* 3435T/T genotype is thought to be associated with higher plasma levels of *MDR1* substrates. However, the effects of *MDR1* polymorphism on the pharmacokinetics and pharmacodynamics of other substrates have not been fully verified.

Recent in vitro data have indicated that lansoprazole is a P-glycoprotein substrate [20], but whether the pharmacoki-

Table 3 Intragastric pH with lansoprazole 30 mg on days 1 and 15 in different *MDR1* C3435T genotype groups

		C/C	C/T	T/T	*P*-value (one-way ANOVA)
Mean 24-h intragastric pH	Control	1.6±0.5	1.9±0.5	1.0±0.1	0.087
	Day 1	3.1±0.8	3.5±1.0	3.8±0.9	0.566
	Day 15	4.7±0.5	4.5±0.3	4.4±0.8	0.737
Percentage time for intragastric pH<4	Control	89.8±5.0	90.5±3.7	96.2±1.3	0.124
	Day 1	64.1±14.5	56.6±17.3	55.2±15.8	0.646
	Day 15	42.4±9.2	65.8±27.4	45.7±16.8	0.164

netics and pharmacodynamics of lansoprazole are affected by the *MDR1* C3435T polymorphism in humans has not been clearly established. Our results here showed that plasma levels in the T/T group were the highest of the three *MDR1* genotype groups, a finding expected based on the Hoffmeyer report [19]. Interestingly, this between-group difference decreased after repeated dosing of lansoprazole, and the kinetic dispositions of lansoprazole in the C/C and C/T groups became closer to those of the T/T group with increasing C_{max}. This observation indicates that lansoprazole inhibits the activity of *MDR1* gradually in the C/C and C/T groups. Further studies are required to verify this finding.

Contrarily, our present study further demonstrated that the *MDR1* C3435T polymorphism did not affect the gastric-acid inhibition attained by lansoprazole on either day 1 or day 15. Although we are unable to explain why *MDR1* genotype was associated with plasma concentration but not intragastric pH, particularly on day 1, we suspect the following: First, because all subjects in the present study had the RM genotype of *CYP2C19*, lansoprazole metabolism in the liver may have been so fast that the influence of *MDR1* genotypic differences on the pharmacokinetics of lansoprazole could not be reflected in the pharmacodynamics. Second, although C_{max} was highest in the T/T group, there was no significant difference in AUC values among the three *MDR1* genotype groups, indicating that plasma lansoprazole levels in the T/T group did not remain high long enough to affect the intragastric pH. This finding could be explained by our previous report, which indicated that the acid-inhibitory effect of PPI depended on the time spent above the threshold concentration, not on the C_{max} [30].

Several reports have cited findings contrary to those of Hoffmeyer. Nakamura et al. [31] suggested that the expression of serum digoxin of *MDR1* mRNA in the duodenum of individuals homozygous for 3435T (T/T) was higher than in individuals with the C/C or C/T genotypes in Japanese subjects. Another meta-analysis review has indicated that *MDR1* C3435T polymorphism does not affect the pharmacokinetics of digoxin or the expression of *MDR1* mRNA [25]. The single SNP in exon 26 (C3435T) is a synonymous SNP, so it does not change the encoded amino acid sequence. However, *MDR1* C3435T has been reported to be in linkage disequilibrium with other common functional nonsynonymous polymorphisms such as *MDR1* exon 21 (G2677A/T, Ala893Thr, or Ala893Ser) [32]. In the present study, the C3435T polymorphism was linked with G2677T and C1236T (a synonymous SNP in exon 12) polymorphisms [27]. In fact, *MDR1* C1236T, G2677T, and C3435T polymorphisms have been reported to be part of a common haplotype [33].

Recent studies have demonstrated that the activity of *MDR1* is related to not only C3435T but also C1236T and G2677A/T polymorphisms, and that haplotypic analysis of these SNPs is important for the precise evaluation of *MDR1* activity. Park et al. reported that the clinical effects of fentanyl were significantly dependent on both *MDR1* C1236T and C3435T polymorphisms [34]. Kim et al. reported that the haplotypic analysis of SNPs at positions 2677 and 3435 was well associated with the pharmacokinetics of amlodipine [35]. In the present study, analysis of the effect of G2677A/T and C3435T haplotype showed that haplotype analysis could not clarify the gene-dose effect on lansoprazole. We therefore believe that analysis of single

Table 4 Pharmacokinetics and intragastric pH between haplotype of *MDR1* G2677A/T and C3435T on days 1 and 15

		GC/GC (*n*=4)	TT/TT (*n*=4)	*P*-value (one-way ANOVA)
Day 1	C_{max} (ng/ml)	850±249	1,157±520	0.329
	$AUC_{0-24\ h}$ (h·ng/ml)	2,736±1,115	3,232±1,204	0.568
	Mean 24-h intragastric pH	3.0±0.9	3.7±1.1	0.340
Day 15	C_{max} (ng/ml)	1,176±104	1,354±697	0.631
	$AUC_{0-24\ h}$ (h·ng/ml)	3,159±1,028	4,433±1,698	0.282
	Mean 24-h intragastric pH	4.7±0.5	4.2±0.7	0.341

SNP of C3435T is sufficient to estimate *MDR1* activity. Ultimately, the function of *MDR1* C3435T polymorphism remains controversial and is confounded by several genetic as well as ethnic and geographic factors.

Miura et al. [36] reported that the C_{max} and $AUC_{0-24\ h}$ of lansoprazole were significantly increased in Japanese patients with the *MDR1* 3435C allele. However, these authors admitted that the effect of this polymorphism in clinical practice seemed negligible, on the basis that these polymorphisms were not associated with gastroesophageal complications in gastroesophageal reflux disease (GERD) patients treated with lansoprazole. We found that plasma lansoprazole levels, as for C_{max}, were highest in the T/T group of the three *MDR1* genotype groups, a finding that was opposite to that seen by Miura et al. However, our results also demonstrated that *MDR1* C3435T polymorphism did not affect the acid inhibition attained by lansoprazole at the standard dose, although a difference in the plasma lansoprazole levels was seen among the three genotype groups on day 1. Moreover, we observed that the *MDR1* genotype-dependent difference in plasma lansoprazole levels decreased and lost statistical significance following repeated dosing, as on day 15. We therefore consider that the effect of *MDR1* C3435T on the pharmacodynamics of lansoprazole may be small in clinical practice because administration of PPIs in GERD patients usually occurs over an extended period of time.

Several limitations of our study warrant mention. First, we did not evaluate the effect of *MDR1* in subjects with the IM and PM genotypes of *CYP2C19*. Since the plasma concentration of lansoprazole depended on the *CYP2C19* genotype status, it would be better to perform the same study in IMs and PMs of CYP2C19. However, the frequency of PMs in Japan is only 19–23% [26], therefore it was difficult to enroll a sufficient number of PM subjects with different *MDR1* genotypes. Second, our study population was a small pool of healthy volunteers, not patients. These results should therefore be considered preliminary.

In conclusion, our study demonstrates that pharmacokinetics of lansoprazole depends on *MDR1* C3435T polymorphism in Japanese subjects, but its pharmacodynamics does not. Interestingly, the impact of *MDR1* C3435T polymorphism on the pharmacokinetics of lansoprazole becomes smaller after repeated doses. These preliminary findings suggest that the *MDR1* polymorphism is of limited relevance in therapeutic regimens involving lansoprazole. To verify the relevance of *MDR1* polymorphism in patients treated with lansoprazole, future studies in clinical practices should include CYP2C19 IMs and PMs as well as RMs.

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Conflict of interest No authors had any conflicts of interest related to this study.

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