CHIRALITY 17:338–344 (2005)

Effect of Clarithromycin on the Enantioselective Disposition of Lansoprazole in Relation to CYP2C19 Genotypes

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ABSTRACT The aim of this study was to examine the effect of clarithromycin, a CYP3A4 inhibitor, on the enantioselective disposition of lansoprazole among three different CYP2C19 genotype groups in healthy Japanese subjects. These subjects included 6 each of homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs), and poor metabolizers (PMs). In the EMs of CYP2C19, clarithromycin markedly increased C_{max} and the $AUC_{0-\infty}$ of (*S*)-lansoprazole and (*S*)-hydroxylansoprazole compared with those of the corresponding (*R*)-enantiomers. Clarithromycin significantly increased C_{max} and the $AUC_{0-\infty}$ of (*S*)-lansoprazole in the homEMs by 110% and 115%, respectively, and in the hetEMs by 105% and 103%, respectively, compared with placebo. Furthermore, clarithromycin slightly prolonged the elimination half-life of (*R*)-lansoprazole in the homEMs and hetEMs but did not alter that of (*S*)-lansoprazole. In the PMs of CYP2C19, clarithromycin significantly increased C_{max} and the $AUC_{0-\infty}$ and significantly prolonged the elimination half-lives of (*R*)- and (*S*)-lansoprazole by 51% and 49%, respectively. The present study suggests that there are significant drug interactions between (*R*)- or (*S*)-lansoprazole and clarithromycin in EMs by inhibiting the CYP3A4-catalyzed sulfoxidation primarily during the first pass, whereas in PMs, the overall metabolism of lansoprazole is inhibited. *Chirality 17:338–344, 2005.*

KEY WORDS: lansoprazole; clarithromycin; enantiomer; CYP2C19; CYP3A4

Lansoprazole [2-{(3-methyl-4-(2,2,2-trifluoethoxy)-2-pyridyl)methyl}sulfinylbenzimidazole] is one of the most widely used proton pump inhibitors that inhibit gastric acid secretion by interacting with (H^+/K^+)-ATPase in gastric parietal cells.[1] Lansoprazole is widely used in *Helicobacter pylori* eradication therapy along with antibacterial agents such as amoxicillin (INN, amoxicilline) and clarithromycin. The use of a triple regime has resulted in high eradication rates in many clinical trials.[2,3] Clarithromycin is mainly metabolized by CYP3A4 in the liver and is a potent inhibitor of CYP3A4 based on in vitro and in vivo studies.[4–6] Lansoprazole is also metabolized by CYP3A4 to lansoprazole sulfone.[7–9] Therefore, a drug interaction is believed to occur when lansoprazole and clarithromycin are co-administered, thereby resulting in an increase in the plasma concentration of lansoprazole, which elevates the eradication rate of *H. pylori*. On the other hand, lansoprazole is metabolized to 5-hydroxylansoprazole mainly by CYP2C19 with only minor involvement by CYP3A4 and CYP2C9.[7,10] This hydroxylation pathway is the main metabolic route of lansoprazole; therefore, its disposition is strongly influenced by the CYP2C19 genetic polymorphism.[11,12] In some subjects with poor metabolizer (PM) status for CYP2C19, lansoprazole metabolism is assumed to be particularly affected by clarithromycin, because the main metabolic pathway of lansoprazole in PMs of CYP2C19 is shifted from CYP2C19 to CYP3A4. In population studies, the PM phenotype of CYP2C19 appears to be present in approximately 1–6% of white subjects,[13–15] 2% of black subjects,[16] and 12–27% of Asian subjects.[13,17–19] For these groups, CYP3A4 is an important lansoprazole-metabolizing enzyme.

Lansoprazole has an asymmetric sulfur atom in its chemical structure and is commercially marketed as a racemic mixture. Both the (*R*)- and (*S*)-enantiomers of lansoprazole inhibit acid formation in isolated canine parietal cells and (H^+/K^+)-ATPase in canine gastric microsomes with nearly the same potency.[20] However,

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Received for publication 7 December 2004; Accepted 9 February 2005
DOI: 10.1002/chir.20159
Published online in Wiley InterScience (www.interscience.wiley.com).

the racemate is an entity with properties quite disparate from those of the two optical isomers. The plasma concentrations of (*R*)-lansoprazole were consistently higher than those of the (*S*)-enantiomer in both EMs and PMs of CYP2C19.[21,22] Such differences between the pharmacokinetics of lansoprazole enantiomers are assumed to be influenced by enantioselective metabolism.[21,23] An in vitro experiment in human liver microsomes showed that intrinsic clearance (V_{max}/K_m), enabling the estimation of the in vivo clearance rate,[24] for the sulfoxidation of (*S*)-lansoprazole is 4-fold higher than that for its (*R*)-enantiomer.[23] Therefore, the inhibition of CYP3A4 activity by clarithromycin that changes the pharmacokinetics of (*S*)-lansoprazole is assumed to be greater than that of the (*R*)-enantiomer and to be strongly influenced by the CYP2C19 genetic polymorphism. Until now, no information about the effect of clarithromycin on the enantioselective disposition of lansoprazole in relation to CYP2C19 genotype status has been published.

In the present study, we examine how clarithromycin affects the metabolism of each lansoprazole enantiomer and to what extent this interaction occurs in relation to CYP2C19 genotype status.

MATERIALS AND METHODS

Reagents and Chemicals

Lansoprazole, its enantiomers, and their metabolites (5-hydroxylansoprazole and lansoprazole sulfone) were purchased from Takeda Pharmaceutical Co. Ltd. (Osaka, Japan). (*S*)-Omeprazole was kindly donated by Astra-Zeneca (Mölndal, Sweden). Oasis HLB extraction cartridges were purchased from Waters (Milford, MA). All solvents used were of HPLC grade (Wako Pure Chemical Industries, Osaka, Japan), and all other reagents and chemicals were purchased from Wako Chemical Industries or Nacalai Tesque (Kyoto, Japan).

Subjects

Eighteen healthy, *H. pylori*-negative Japanese subjects (six homEMs, six hetEMs, and six PMs) were selected to participate in this study. The subjects enrolled in the present study are the same as those who participated in our previous study.[22] Their mean age was 25.1 ± 3.8 years (range 21–34 years), and their mean weight was 56.6 ± 13.3 kg (range 40–86 kg). There were no differences among the three CYP2C19 genotypes—homEMs, hetEMs, and PMs—in subject profiles, including age (24.7 ± 3.8, 25.0 ± 4.5, and 25.7 ± 3.6 years, respectively), body weight (57.2 ± 15.6, 53.0 ± 10.5, and 59.5 ± 5.0 kg, respectively), body mass index (20.9 ± 3.8, 20.5 ± 2.5, and 21.3 ± 3.5 kg/m^2, respectively), and male/female ratios (3/3 each). None of the subjects had a history of significant medical illness or hypersensitivity to any drug. All subjects were nonsmokers. None had taken any drug for at least 1 week before and during the study. The study protocol was approved by the Ethics Committee of Hirosaki University Hospital, and all subjects gave their written informed consent before participating.

Study Protocols

A randomized, double-blind placebo-controlled crossover study design was conducted at intervals of 2 weeks. After clarithromycin (400 mg) in capsule form containing two tablets (Clarith®, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan) or matched placebo (in capsule form with the same appearance and size as that of clarithromycin) was given orally twice a day (9 am, 9 pm) for 6 days, each subject received an oral dose of 60 mg of lansoprazole (Takepron®, Takeda Pharmaceutical Co., Ltd.) with a glass of tap water at 9 am. Venous blood samples were taken for the determination of the plasma concentrations of lansoprazole enantiomers and their metabolites before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h after dosing. The samples were centrifuged at 3,000*g* immediately after collection and stored at −80°C until they were analyzed. All subjects fasted for 10 h before administration of lansoprazole and had a standard meal 4 h later. Beverages containing alcohol and caffeine were forbidden during the test period.

CYP2C19 Genotyping

Genotyping to identify the CYP2C19 wild-type gene and two mutated alleles, CYP2C19*2 in exon 5 and CYP2C19*3 in exon 4, were performed using a polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method.[25] The CYP2C19 genotype analysis revealed five different patterns as follows: *1/*1 in 6 subjects, *1/*2 in 3, *1/*3 in 3, *2/*2 in 5 and *2/*3 in 1. These subjects were divided into 3 groups: homEMs (*1/*1, $n = 6$), hetEMs (*1/*2 and *1/*3, $n = 6$), and PMs (*2/*2 and *2/*3, $n = 6$).

Analysis of Lansoprazole Enantiomers and Their Metabolites in Plasma

The plasma concentration of lansoprazole, its enantiomers and their metabolites were determined according to the HPLC method of Miura et al.[22,26] In brief, after (*S*)-omeprazole (20 ng) in methanol (10 μl) was added to plasma samples (100 μl) as an internal standard, the samples were diluted with water (1.0 ml), and the solutions were briefly mixed. Each mixture was applied to an Oasis HLB® extraction cartridge that had been previously activated with methanol and water (1.0 ml each). The cartridge was then washed with 40% methanol in water (1.0 ml), and then eluted with 80% methanol in water (1.0 ml). The eluate was evaporated to dryness in a vacuum at 60°C with a rotary evaporator (Iwaki, Tokyo, Japan). The residue was dissolved in 50 μl of methanol and 50 μl of mobile phase; and an aliquot (50 μl) of the solution was then injected into the HPLC apparatus. The apparatus used for HPLC was a Model 510 chromatography pump (Waters Co.) equipped with a Waters 486 ultraviolet detector. The wavelength was set at 285 nm. Test samples were introduced using a Waters 712 WISP autosampler with an effective volume of 50 μl. The HPLC column used was a Chiral CD-Ph (250 mm × 4.6 mm i.d., Shiseido Co., Ltd., Tokyo, Japan); and the mobile phase which consisted of 0.5 M $NaClO_4$–acetonitrile–methanol (60:30:10, v/v/v), was degassed in an ultrasonic bath prior to use. A flow rate

of 0.5 ml/min was used at ambient temperature, and the wavelength was set at 285 nm. The lower limit of quantitation for this assay was 10 ng/ml for each enantiomer of lansoprazole and 5-hydroxylansoprazole, whereas it was 5 ng/ml for lansoprazole sulfone. The coefficient of variation of the inter- and intra-day assays ($n = 6$) was <8.0%, and the accuracy ($n = 6$) was within 8.4% for all analytes (concentration range of 10–4,000 ng/ml).[25] Retention times for (*R*)-5-hydroxylansoprazole, (*S*)-5-hydroxylansoprazole (*S*)-omeprazole, lansoprazole sulfone, (*R*)-lansoprazole, and (*S*)-lansoprazole were 17.0, 18.5, 27.5, 30.0, 31.6, and 36.6 min, respectively.

Identification of Elution Orders of 5-Hydroxylansoprazole Enantiomers

The elution orders of 5-hydroxylansoprazole enantiomers in the HPLC chromatogram were identified by the in vitro metabolism of (*R*)- or (*S*)-lansoprazole using human CYP2C19 expressed in a cell line (Gentest Corporation, Woburn, MA). Incubations were carried out with the reconstituted human liver microsomes in 5-ml test tubes using a shaking water bath for 30 min at 37°C. A typical incubation mixture consisted of a cofactor solution (100 μl), microsomal CYP2C19 preparation (50 μl, 0.5 mg protein), and substrate (5 μl, 13.5 μM for (*R*)- or (*S*)-lansoprazole) in a total volume of 0.2 ml. The cofactor solution consisted of $NADP^+$ (1.3 mM), glucose-6-phosphate (3.3 mM), glucose-6-phosphate dehydrogenase (0.4 unit), and magnesium chloride (3.3 mM) in sodium phosphate buffer (0.1 M, pH 7.4). The metabolic reaction was initiated by the addition of the cofactor solution and terminated by immersion in an ice bath. Before the extraction, (*S*)-omeprazole (20 ng) in methanol (10 μl) was added as an internal standard to the incubation mixture. Each mixture was applied to an Oasis HLB® extraction cartridge as described above.

Pharmacokinetic Analysis

Pharmacokinetic analysis of the lansoprazole enantiomers and their metabolites was carried out by a standard noncompartmental method using WinNonlin (Pharsight Co., CA, version 4.0.1). The elimination half-life was obtained using log–linear regression of the terminal phase of the concentration–time data with at least three sampling points (elimination half life = $\ln 2/k_e$; k_e = elimination rate constant). The total area under the observed plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule. The extrapolation of AUC from the last measurable concentration (C_t) to infinity ($AUC_{t-\infty}$) was performed by adding the value C_t/k_e (where C_t = plasma concentration at t h after lansoprazole administration). The maximum plasma concentration (C_{max}) and time required to reach the peak (t_{max}) were obtained directly from the profile.

Statistical Analysis

All results were expressed as mean values ± SD. Statistical comparisons of parameters were made by one-way analysis of variance (ANOVA) and supplemented with the multiple comparison procedure of Fisher in the Stat View program (SAS Institute, Cary, NC, version 5.0). P values of less than 0.05 were considered statistically significant.

RESULTS

The plasma concentrations and the mean C_{max} and $AUC_{0-\infty}$ of the (*R*)- and (*S*)-enantiomers of lansoprazole were increased by clarithromycin in the three different CYP2C19 genotype groups (Fig. 1). Furthermore, clarithromycin significantly prolonged the elimination half-life of (*R*)- and (*S*)-lansoprazole in the PMs from 5.0 to 7.7 h ($P < 0.01$) and from 1.6 to 2.4 h ($P < 0.01$), respectively. In the homEMs and hetEMs, clarithromycin slightly prolonged the half-life of the (*R*)-enantiomer but did not change that of the (*S*)-enantiomer (Table 1). The C_{max} values of (*S*)-lansoprazole by clarithromycin in the homEMs, hetEMs, and PMs were approximately 1.8-, 1.7-, and 1.5-fold higher, respectively, compared with those of the corresponding (*R*)-enantiomer. On the other hand, clarithromycin decreased C_{max} and the $AUC_{0-\infty}$ for lansoprazole sulfone in the three genotype groups and significantly prolonged t_{max} and the elimination half-life in the PMs, whereas there was no change in the homEMs and hetEMs (Table 2). In addition, clarithromycin increased C_{max} and the $AUC_{0-\infty}$ for the (*R*)- and (*S*)-enantiomers of 5-hydroxylansoprazole in the homEMs and hetEMs but not in the PMs (Table 2). Mean changes in the C_{max} and $AUC_{0-\infty}$ values for (*S*)-5-hydroxylansoprazole induced by clarithromycin in the homEMs and hetEMs were higher compared to those of the corresponding (*R*)-enantiomer. The AUC ratios of (*S*)-5-hydroxylansoprazole to (*S*)-lansoprazole were increased by clarithromycin in the homEMs from 0.651 to 0.932 and, were not altered in the hetEMs, but were markedly decreased in the PMs, from 0.079 to 0.020. On the other hand, those of the (*R*)-enantiomer were not altered in the homEMs and hetEMs but were decreased by clarithromycin in the PMs, from 0.006 to 0.002 (Table 2).

DISCUSSION

This is the first report on the effect of clarithromycin on the pharmacokinetics of lansoprazole enantiomers in relation to CYP2C19 genotype status. In the present study, we could not directly determine the magnitude of the contribution of CYP3A4 to the sulfoxidation of each lansoprazole enantiomer because the sulfone metabolite is achiral. However, clarithromycin enhanced the hydroxylation of (*S*)-lansoprazole in homEMs and hetEMs compared with the (*R*)-enantiomer. This suggests that the contribution of CYP3A4 to the metabolism of (*S*)-lansoprazole is greater than that of the (*R*)-enantiomer. This is in agreement with a previous in vitro study in which the intrinsic clearance of (*S*)-lansoprazole sulfoxidation by cDNA-expressed CYP3A4 was greater than that of the (*R*)-enantiomer.[10] Furthermore, it has been reported that the sulfide, resulting from the nonenzymatic reduction of lansoprazole, is also present in a smaller amount (1.5%).[27] The formed sulfide may be oxidized enzymatically to lansoprazole sulfone, and the stereoselectivity of this oxidation may contribute to inversion at the chiral centrer.

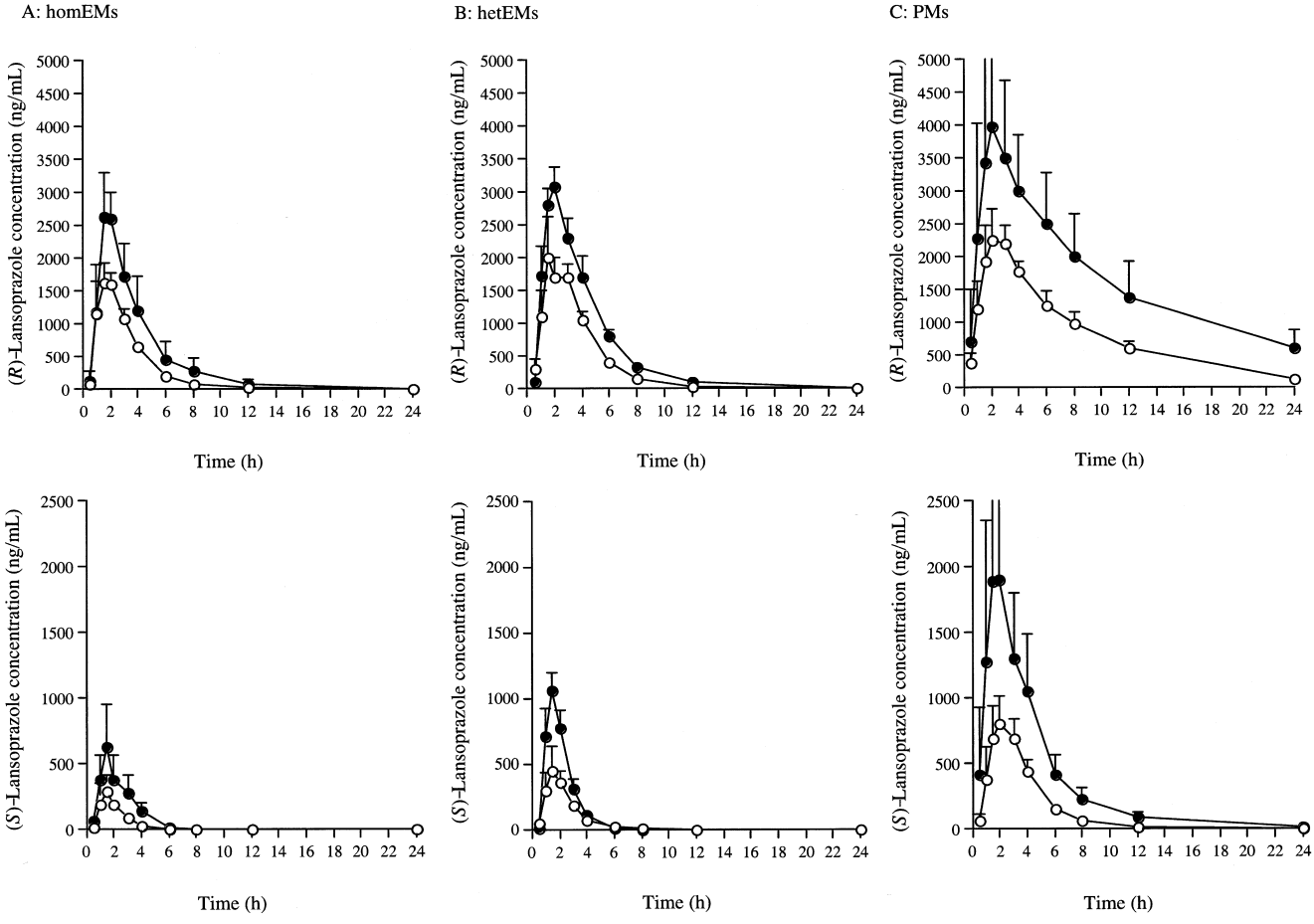

Fig. 1. Influence of clarithromycin on disposition of (*R*)-lansoprazole (upper panel) and (*S*)-lansoprazole (lower panel) in homozygous EMs (**A**), heterozygous EMs (**B**), and PMs (**C**). Subjects received a single oral dose of 60 mg of racemic lansoprazole following administration of placebo (open circles) or 400 mg of clarithromycin (solid circles) twice a day for 6 days. The results are plasma concentrations shown as the mean ± SD.

However, one in vitro study reported that the chiral inversions of (*R*)- to (*S*)- and (*S*)- to (*R*)-lansoprazole did not occur at clinically relevant concentrations.[23]

Clarithromycin significantly increased the C_{max} and $AUC_{0-\infty}$ of (*R*)- and (*S*)-lansoprazole in the homEMs and hetEMs. In addition, it prolonged slightly the elimination half-life of the (*R*)-enantiomer but did not alter that of the (*S*)-enantiomer. Because of this, it seems that clarithromycin inhibits the CYP3A4-mediated sulfoxidation of lansoprazole mainly during the first pass. CYP3A4 is present in considerable quantities in the small-intestinal mucosa,[28–30] and intestinal CYP3A4 has been shown to play a major role in the interaction between clarithromycin and midazolam.[5] Clarithromycin inhibits intestinal CYP3A rather than that in the liver CYP3A.[5] Therefore, in subjects with CYP2C19*1, it is probable that the intestinal CYP3A4 also plays an important role in the interaction of clarithromycin with lansoprazole enantiomers. On the other hand, the elimination of (*S*)-lansoprazole in EMs of CYP2C19 is not affected by clarithromycin, and it seems that (*S*)-lansoprazole is mainly catalyzed by CYP2C19 as opposed to CYP3A4.[31,32] In PMs of CYP2C19, clarithromycin significantly increases C_{max} and the $AUC_{0-\infty}$ and prolongs the elimination half-lives of (*R*)- and (*S*)-lansoprazole by 51% ($P < 0.01$) and 49% ($P < 0.01$), respectively. Thus, clarithromycin inhibits the overall metabolism of (*R*)- and (*S*)-lansoprazole in the PMs of CYP2C19. Furthermore, several previous studies have shown that clarithromycin is an inhibitor of P-glycoprotein.[33–36] One in vitro study found that lansoprazole is a substrate of P-glycoprotein.[37] Therefore, it is possible that the inhibition of P-glycoprotein by clarithromycin contributes to this interaction. However, it is unknown whether the affinity of lansoprazole for P-glycoprotein differs between the enantiomers.

For (*S*)-lansoprazole, clarithromycin significantly increased C_{max} and the $AUC_{0-\infty}$ of (*S*)-5-hydroxylansoprazole by 232% and 278%, respectively, in the homEMs, and increased the AUC ratio of (*S*)-5-hydroxylansoprazole to (*S*)-lansoprazole by 95% in homEMs. Furthermore, clarithromycin also increased C_{max} and the $AUC_{0-\infty}$ of (*S*)-5-hydroxylansoprazole in hetEMs but did not change the AUC ratio of (*S*)-5-hydroxylansoprazole to (*S*)-lansoprazole. Our data suggests that the CYP2C19-mediated 5-hydroxylation activity of (*S*)-lansoprazole increased by clarithromycin is higher in homEMs than in hetEMs. On

TABLE 1. Pharmacokinetic parameters of (*R*)- and (*S*)-lansoprazole with clarithromycin in three CYP2C19 genotype groups[a]

	Homozygous EMs			Heterozygous EMs			PMs		
Study group	Placebo	CAM	Change (%)	Placebo	CAM	Change (%)	Placebo	CAM	Change (%)
(*R*)-Lansoprazole									
C_{max} (ng/ml)	1957 ± 413	3009 ± 542	60 ± 54	2196 ± 405	3209 ± 471*	63 ± 49	2516 ± 357	4201 ± 1215*	59 ± 64
t_{max} (h)	1.9 ± 0.6	2.0 ± 0.6	7 ± 23	2.3 ± 0.8	2.0 ± 0.6	−3 ± 34	2.4 ± 0.9	2.25 ± 0.88	−3 ± 52
Half-life (h)	1.3 ± 0.3	1.5 ± 0.4	16 ± 40	1.5 ± 0.2	1.9 ± 0.2	23 ± 14	5.0 ± 1.0	7.7 ± 1.0**	51 ± 31
$AUC_{0-\infty}$ (ng·h/ml)	5,009 ± 919	9,761 ± 2,891	85 ± 89	7,300 ± 1,008	12,498 ± 878**	80 ± 45	20,132 ± 3,570	46,944 ± 14,517**	142 ± 104
(*S*)-Lansoprazole									
C_{max} (ng/ml)	337 ± 135	712 ± 261*	110 ± 69	528 ± 166	1,081 ± 264*	105 ± 91	1,156 ± 253	2,171 ± 750*	90 ± 96
t_{max} (h)	1.7 ± 0.7	1.6 ± 0.2	−3 ± 27	1.8 ± 0.7	1.5 ± 0.3	−2 ± 42	1.9 ± 0.6	1.8 ± 0.3	−4 ± 23
Half-life (h)	0.6 ± 0.1	0.6 ± 0.1	2 ± 27	0.7 ± 0.2	0.6 ± 0.1	−4 ± 46	1.6 ± 0.5	2.4 ± 1.0**	49 ± 34
$AUC_{0-\infty}$ (ng·h/ml)	524 ± 189	1,191 ± 476*	115 ± 84	967 ± 224	1970 ± 507*	103 ± 72	3,892 ± 992	8,278 ± 2,993*	108 ± 80

*$P < 0.05$, **$P < 0.01$ compared with placebo group.
[a]The values are presented as the mean ± SD. C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $AUC_{0-\infty}$, area under the plasma concentration–time curve, from 0 to infinity; EM, extensive metabolizer; PM, poor metabolizer; CAM, clarithromycin.

TABLE 2. Pharmacokinetic parameters of lansoprazole sulfone and 5-hydroxylansoprazole enantiomers with clarithromycin in three CYP2C19 genotype groups[a]

	Homozygous EMs			Heterozygous EMs			PMs		
Study group	Placebo	CAM	Change (%)	Placebo	CAM	Change (%)	Placebo	CAM	Change (%)
Lansoprazole sulfone									
C_{max} (ng/ml)	112 ± 106	28.2 ± 6.67	−84 ± 10	184 ± 142	30.0 ± 24.2*	−73 ± 25	568 ± 277	129 ± 83**	−80 ± 10
t_{max} (h)	1.8 ± 0.7	2.0 ± 0.9	1 ± 15	2.0 ± 0.8	1.9 ± 0.7	7 ± 63	3.2 ± 1.0	8.0 ± 0.0**	153 ± 87
Half-life (h)	0.6 ± 0.2	0.4 ± 0.2	−35 ± 38	0.6 ± 0.2	0.5 ± 0.2	−9 ± 68	7.1 ± 3.4	12.9 ± 4.0**	52 ± 23
$AUC_{0-\infty}$ (ng·h/ml)	197 ± 204	40 ± 31	−88 ± 11	368 ± 239	44 ± 24*	−82 ± 12	7,756 ± 4,855	3,306 ± 2,259**	−58 ± 24
(*R*)-5-Hydroxylansoprazole									
C_{max} (ng/ml)	91 ± 35	122 ± 62	20 ± 28	50 ± 21	100 ± 34*	78 ± 63	26 ± 8	23 ± 4	−2 ± 35
t_{max} (h)	1.8 ± 0.7	2.1 ± 0.6	23 ± 52	2.4 ± 0.7	2.5 ± 0.7	18 ± 56	2.8 ± 1.7	2.1 ± 0.6	2 ± 21
Half-life (h)	1.0 ± 0.2	1.7 ± 0.5	62 ± 23	2.4 ± 0.8	1.7 ± 0.8	−41 ± 26	1.2 ± 0.3	1.4 ± 0.3	29 ± 37
$AUC_{0-\infty}$ (ng·h/ml)	237 ± 128	479 ± 281*	100 ± 66	230 ± 113	392 ± 209	90 ± 87	85 ± 48	65 ± 10	−3 ± 27
$AUC_{(R)\text{-OH-LAN}}/AUC_{(R)\text{-LAN}}$	0.049 ± 0.016	0.056 ± 0.028	38 ± 63	0.036 ± 0.022	0.033 ± 0.015	30 ± 124	0.006 ± 0.007	0.002 ± 0.001	−46 ± 40
(*S*)-5-Hydroxylansoprazole									
C_{max} (ng/ml)	128 ± 69	389 ± 199**	232 ± 159	129 ± 26	310 ± 140**	146 ± 70	39 ± 21	36 ± 13	−2 ± 16
t_{max} (h)	1.6 ± 0.2	1.7 ± 0.3	7 ± 15	2.3 ± 0.8	2.5 ± 1.0	3 ± 82	1.9 ± 0.6	2.0 ± 0.6	1 ± 32
Half-life (h)	0.7 ± 0.2	1.0 ± 0.4	72 ± 70	1.0 ± 0.4	1.1 ± 0.3	19 ± 42	1.5 ± 0.5	1.2 ± 0.4	−12 ± 30
$AUC_{0-\infty}$ (ng·h/ml)	246 ± 145	896 ± 565**	278 ± 201	355 ± 106	977 ± 547**	200 ± 149	142 ± 110	105 ± 68	−17 ± 64
$AUC_{(S)\text{-OH-LAN}}/AUC_{(S)\text{-LAN}}$	0.651 ± 0.413	0.932 ± 0.558	95 ± 72	0.500 ± 0.259	0.535 ± 0.260	14 ± 18	0.079± 0.111	0.020 ± 0.018	−38 ± 34

*$P < 0.05$, **$P < 0.01$ compared with placebo group.
[a]The values are presented as the mean ± SD. C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $AUC_{0-\infty}$, area under the plasma concentration–time curve, from 0 to infinity; EM, extensive metabolizer; PM, poor metabolizer; CAM, clarithromycin.

the other hand, in PMs who lacked CYP2C19 activity, clarithromycin did not alter C_{max} and $AUC_{0-\infty}$ of (*S*)-5-hydroxylansoprazole but did produce increases in C_{max} and $AUC_{0-\infty}$ and significantly prolonged the half-life of (*S*)-lansoprazole. Because of this, we assume that the hydroxylation of lansoprazole to 5-hydroxylansoprazole in PMs might be mediated by CYP2C9.[10]

Furuta et al. reported that eradication rates for *H. pylori* infection using triple therapy depend on the CYP2C19 genotypes of patients.[38] Treatment with daily doses of lansoprazole (60 mg) or omeprazole (40 mg), amoxicillin (1,500 mg), and clarithromycin (600 mg) for 1 week gave responses of 72.7%, 92.1%, and 97.8% in homEMs, hetEMs, and PMs, respectively. The differences in the eradication rates of *H. pylori* using a PPI among the different CYP2C19 genotypes are believed to arise from different plasma concentrations of PPI among the different genotype groups.[39] Although the contribution of each lansoprazole enantiomer to the eradication rates for *H. pylori* is not known, the disposition of each enantiomer of lansoprazole with clarithromycin is also significantly influenced by CYP2C19 genetic polymorphism. As noted above, the interaction between the PPI and clarithromycin is believed to underlie the high cure rate for the eradication of *H. pylori*.[39] In our present study, the mean $AUC_{0-\infty}$ values of (*R*)- and (*S*)-lansoprazole for the EMs also receiving clarithromycin were much lower than those in the PMs who did not take clarithromycin. On the other hand, in previous studies, the disposition of (*S*)-lansoprazole is greatly affected by CYP2C19 genetic polymorphism[22,32] and is metabolized more by CYP3A4.[10,23] Furthermore, the elimination half-life of (*S*)-lansoprazole is very short compared with its (*R*)-enantiomer.[22] (*S*)-Lansoprazole is not optically stable in vivo. Therefore, similar to a previous in vitro study,[20] if such pharmacodynamic effects as the intragastric pH of the (*R*)- and (*S*)-enantiomers of lansoprazole are identical in the human body, then it is adapted clinically only by (*R*)-lansoprazole. Therefore, EMs of CYP2C19 might be receiving as much as twice the average daily dose as (*R*)-lansoprazole. We suggest that (*R*)-lansoprazole should be developed as a single-isomer PPI, as is the case with esomeprazole, the (*S*)-isomer of the PPI omeprazole.

In conclusion, this drug interaction is more marked between (*S*)-lansoprazole and clarithromycin than between (*R*)-lansoprazole and clarithromycin. In EMs of CYP2C19, clarithromycin significantly increased the plasma concentration of lansoprazole, probably by inhibiting the CYP3A4-mediated sulfoxidation mainly during the first pass. On the other hand, in PMs of CYP2C19, clarithromycin markedly increased the plasma concentrations of (*R*)- and (*S*)-lansoprazole by inhibiting the overall metabolism of lansoprazole.

LITERATURE CITED

1. Nagaya H, Satoh H, Maki Y. Possible mechanism for the inhibition of acid formation by the proton pump inhibitor AG-1749 in isolated canine parietal cells. J Pharmacol Exp Ther 1990;252:1289–1295.
2. Miwa H, Murai T, Sato K, Ohkura R, Yamada T, Nagahara A, Ohtaka K, Minowa T, Kurosawa A, Sato N. Comparison of the efficacy of 400 mg and 800 mg of clarithromycin used with lansoprazole and amoxicillin in eradication regimens for *Helicobacter pylori* infection in a Japanese population. J Gastroenterol 2000;35:536–539.
3. Schwartz H, Krause R, Sahba B, Haber M, Weissfeld A, Rose P, Siepman N, Freston J. Triple versus dual therapy for eradicating *Helicobacter pylori* and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. Am J Gastroenterol 1998;93:584–590.
4. Rodrigues AD, Roberts EM, Mulford DJ, Yao Y, Ouellet D. Oxidative metabolism of clarithromycin in the presence of human liver microsomes. Major role for the cytochrome P4503A (CYP3A) subfamily. Drug Metab Dispos 1997;25:623–630.
5. Gorski JC, Jones DR, Haehner-Daniels BD, Hamman MA, O'Mara Jr EM, Hall SD. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. Clin Pharmacol Ther 1998;64:133–143.
6. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. Br J Clin Pharmacol 2000;50:285–295.
7. Pearce RE, Rodrigues AD, Goldstein JA, Parkinson A. Identification of the human P450 enzymes involved in lansoprazole metabolism. J Pharmacol Exp Ther 1996;277:805–816.
8. Katsuki H, Nakamura C, Arimori K, Fujiyama S, Nakano M. Katsuki H. Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects. Eur J Clin Pharmacol 1997;52:391–396.
9. Pichard L, Curi-Pedrosa R, Bonfils C, Jacqz-Aigrain E, Domerque J, Joyeux H, Cosme J, Guengerich FP. Oxidative metabolism of lansoprazole by human liver cytochromes P450. Mol Pharmacol 1995;47:410–418.
10. Kim KA, Kim MJ, Park JY, Shon JH, Yoon YR, Lee SS, Liu KH, Chun JH, Hyun MH, Shin JG. Stereoselective metabolism of lansoprazole by human liver cytochrome P450 enzymes. Drug Metab Dispos 2003;31:1227–1234.
11. Sohn DR, Kwon JT, Kim HK, Ishizaki T. Metabolic disposition of lansoprazole in relation to the *S*-mephenytoin 4′-hydroxylation phenotype status. Clin Pharmacol Ther 1997;61:574–582.
12. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors—emphasis on rabeprazole. Aliment Pharmacol Ther 1999;13:27–36.
13. Bertilsson L, Lou YQ, Du YL, Liu Y, Kuang TY, Liao XM, Wang KY, Reviriego J, Iselius L, Sjoqvist F. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and *S*-mephenytoin. Clin Pharmacol Ther 1992;51:388–397.
14. Wedlund PJ, Aslanian WS, McAllister CB, Wilkinson GR, Branch RA. Mephenytoin hydroxylation deficiency in Caucasians: frequency of a new oxidative drug metabolism polymorphism. Clin Pharmacol Ther 1984;36:773–780.
15. Goldstein JA, Ishizaki T, Chiba K, de Morais SM, Bell D, Krahn PM, Evans DA. Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizer phenotype in various Oriental, Caucasian, Saudi Arabian and American black populations. Pharmacogenetics 1997;7:59–64.
16. Marinac JS, Balian JD, Foxworth JW, Willsie SK, Daus JC, Owen R, Flockhart DA. Determination of CYP2C19 phenotype in black Americans with omeprazole: correlation with genotype. Clin Pharmacol Ther 1996;60:138–144.
17. Roh HK, Dahl ML, Tybring G, Yamada H, Cha YN, Bertilsson L. CYP2C19 genotype and phenotype determined by omeprazole in a Korean population. Pharmacogenetics 1996;6:547–551.
18. Kimura M, Ieiri I, Wada Y, Mamiya K, Urae A, Iimori E, Sakai T, Otsubo K, Higuchi S. Reliability of the omeprazole hydroxylation index for CYP2C19 phenotyping: possible effect of age, liver disease and length of therapy. Br J Clin Pharmacol 1999;47:115–119.
19. Nakamura K, Goto F, Ray WA, McAllister CB, Jacqz E, Wilkinson GR, Branch RA. Interethnic differences in genetic polymorphism of

debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. Clin Pharmacol Ther 1985;38:402–408.

20. Nagaya H, Inatomi N, Nohara A, Satoh H. Effects of the enantiomers of lansoprazole (AG-1749) on (H^++K^+)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells. Biochem Pharmacol 1991;42:1875–1878.
21. Kim K, Shon J, Park J, Yoon Y, Kim M, Yun D, Kim M, Cha I, Hyun M, Shin J. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. Clin Pharmacol Ther 2002;72:90–99.
22. Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. Eur J Clin Pharmacol 2004;60:623–628.
23. Katsuki H, Hamada A, Nakamura C, Arimori K, Nakano M. Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of lansoprazole by human liver microsomes. Eur J Clin Pharmacol 2001;57:709–715.
24. Rane A, Wilkinson GR, Shand DG. Prediction of hepatic extraction ratio from in vivo measurement of intrinsic clearance. J Pharmacol Exp Ther 1977;200:420–424.
25. De Morais SM, Wilkinson GR, Blaisdell J, Meyer UA, Nakamura K, Goldstein JA. Identification of a new genetic defect responsible for the polymorphism of (*S*)-mephenytoin metabolism in Japanese. Mol Pharmacol 1994;46:594–598.
26. Miura M, Tada H, Suzuki T. Simultaneous determination of lansoprazole enantiomers and their metabolites in plasma by liquid chromatography with solid-phase extraction. J Chromatogr B 2004;804:389–395.
27. Delhotal-Landes B, Cournot A, Vermerie N, Dellatolas F, Benoit M, Flouvat B. The effect of food and antacids on lansoprazole absorption and disposition. Eur J Drug Metab Pharmacokinet 1991;3:315–320.
28. Kivisto KT, Bookjans G, Fromm MF, Griese EU, Munzel P, Kroemer HK. Expression of CYP3A4, CYP3A5 and CYP3A7 in human duodenal tissue. Br J Clin Pharmacol 1996;42:387–389.
29. Zhang QY, Dunbar D, Ostrowska A, Zeisloft S, Yang J, Kaminsky LS. Characterization of human small intestinal cytochromes P-450. Drug Metab Dispos 1999;27:804–809.
30. Kolars JC, Lown KS, Schmiedlin-Ren P, Ghosh M, Fang C, Wrighton SA, Merion RM, Watkins PB. CYP3A gene expression in human gut epithelium. Pharmacogenetics 1994;4:247–259.
31. Yasui-Furukori N, Saito M, Uno T, Takahata T, Sugawara K, Tateishi T. Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. J Clin Pharmacol 2004;44:1223–1229.
32. Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes in the presence of fluvoxamine. Br J Clin Pharmacol 2005; in press.
33. Wakasugi H, Yano I, Ito T, Hashida T, Futami T, Nohara R, Sasayama S, Inui K. Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. Clin Pharmacol Ther 1998;64:123–128.
34. Rengelshausen J, Goggelmann C, Burhenne J, Riedel KD, Ludwig J, Weiss J, Mikus G, Walter-Sack I, Haefeli WE. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin–clarithromycin interaction. Br J Clin Pharmacol 2003;56:32–38.
35. Tanaka H, Matsumoto K, Ueno K, Kodama M, Yoneda K, Katayama Y, Miyatake K. Effect of clarithromycin on steady-state digoxin concentrations. Ann Pharmacother 2003;37:178–181.
36. Kurata Y, Ieiri I, Kimura M, Morita T, Irie S, Urae A, Ohdo S, Ohtani H, Sawada Y, Higuchi S, Otsubo K. Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. Clin Pharmacol Ther 2002;72:209–219.
37. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol 2001;364:551–557.
38. Furuta T, Shirai N, Takashima M, Xiao F, Hanai H, Sugimura H, Ohashi K, Ishizaki T, Kaneko E. Effect of genotypic differences in CYP2C19 on cure rates for *Helicobacter pylori* infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158–168.
39. Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. Pharmacogenomics 2004;5:181–202.