—Reviews—

Enantioselective Disposition of Lansoprazole and Rabeprazole in Human Plasma

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Lansoprazole is extensively metabolized by CYP2C19 and CYP3A4 in the liver, whereas rabeprazole is primarily converted non-enzymatically to rabeprazole-thioether, with only some being oxidized by CYP2C19 and CYP3A4. Lansoprazole and rabeprazole possess asymmetric sulfur in their chemical structure and have typically been used clinically as a racemic mixture. This article reviews the pharmacokinetic differences between enantiomers of lansoprazole and rabeprazole in relation to the CYP2C19 genotypes. In our studies in healthy Japanese subjects, the magnitude of contribution of each lansoprazole enantiomer for CYP2C19 was greater than that for CYP3A4. CYP2C19 influenced the disposition of (*S*)-lansoprazole to a greater extent than the (*R*)-enantiomer. The *R*/*S* ratios for the AUC of lansoprazole in CYP2C19 homEMs, hetEMs and PMs was 12.7, 8.5 and 5.8, respectively. On the other hand, (*R*)-rabeprazole disposition was influenced to a greater degree by CYP2C19 genetic polymorphisms than (*S*)-rabeprazole. However, the *R*/*S* ratios for the AUC of rabeprazole in CYP2C19 homEMs, hetEMs and PMs was only 1.8, 2.2 and 2.4, respectively, suggesting a lesser effect of CYP2C19 polymorphisms on the stereoselective disposition of rabeprazole compared to lansoprazole. Such a difference in the AUC between rabeprazole enantiomers is likely to be dependent on stereoselectivity in the CYP3A4-mediated metabolic conversion from rabeprazole-thioether to rabeprazole. Both enantiomers of these PPIs have been reported to possess equal potency. Therefore, particularly with lansoprazole, the use of (*R*)-lansoprazole alone would be highly desirable for use in clinical applications.

Key words——lansoprazole; rabeprazole; enantiomer; CYP2C19; CYP3A4

INTRODUCTION

Lansoprazole and rabeprazole are proton pump inhibitors (PPIs) that inhibit gastric acid secretion by interacting with H^+/K^+-ATPase in gastric parietal cells.[1—5] Lansoprazole is extensively metabolized in the liver to 5-hydroxylansoprazole and lansoprazole sulfone by CYP2C19 and CYP3A4, respectively (Fig. 1).[6—8] On the other hand, rabeprazole is primarily converted non-enzymatically to rabeprazole-thioether; however, some rabeprazole is oxidized to desmethylrabeprazole and rabeprazole sulfone by CYP2C19 and CYP3A4, respectively (Fig. 1).[9—12] Therefore, CYP2C19 contributes less to the overall metabolism of rabeprazole compared to lansoprazole, and is less influenced by CYP2C19 genetic polymorphisms.[13] Genotypes of CYP2C19 are classified into three groups: homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs), and poor metabolizers (PMs). The pharmacokinetics of PPIs differ among the different CYP2C19 genotype groups. In some subjects that are PMs of CYP2C19, the CYP3A4 inhibitor is assumed to particularly affect the metabolism of lansoprazole and rabeprazole, since the main metabolic pathway of these PPIs is shifted from CYP2C19 to CYP3A4.

Lansoprazole and rabeprazole possess asymmetric sulfur in their chemical structure and have been clinically used as a racemic mixture (Fig. 1). Both enantiomers of these PPIs have been shown to possess equal potency *in vitro*.[2] Generally, the pharmacokinetics of enantiomers of chiral compounds differ in the human body. In omeprazole, which is one class of PPIs, the plasma concentrations of (*S*)-omeprazole are higher and less influenced by CYP2C19 genetic polymorphisms compared to those of (*R*)-omeprazole or racemic omeprazole.[14—16] This finding has led to the development of esomeprazole, the (*S*)-enantiomer of omeprazole, as the first single enantiomer PPI. In this study, we investigated the pharmacokinetic differences between enantiomers of lansoprazole and rabeprazole in relation to CYP2C19 genotypes.

ANALYTICAL METHODS

Analysis of Lansoprazole Enantiomers and Their Metabolites in Human Plasma The stereoselective differences in the biotransformation of lansoprazole

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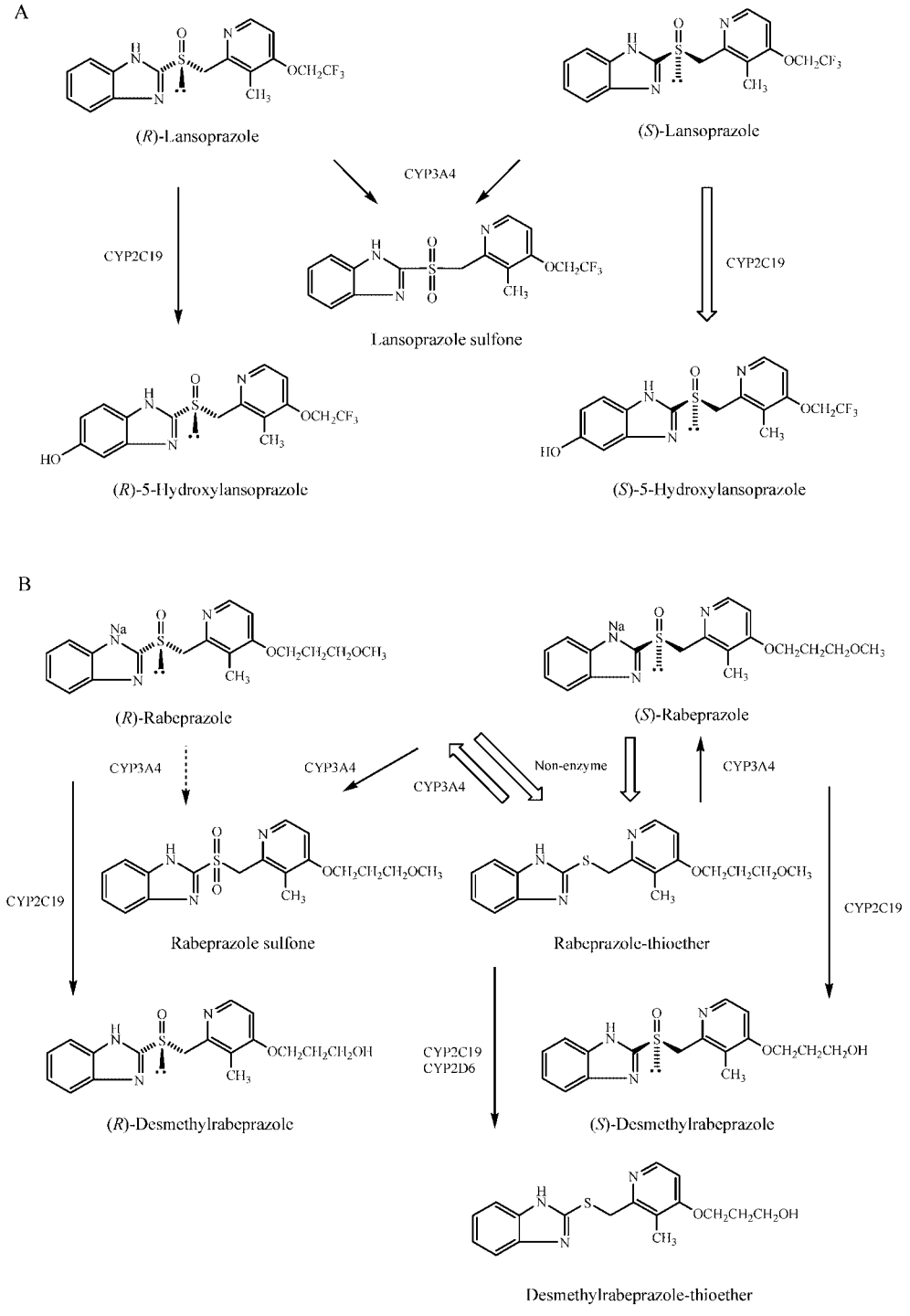

Fig. 1. Metabolic Pathways of the Enantiomers of Lansoprazole (A) and Rabeprazole (B)
A big arrow shows the main metabolic pathway.

enantiomers in human plasma have been studied by high-performance liquid chromatography (HPLC) using chiral columns (Chiralcel OD or Chiralpak AS, Daicel Chemical Co.).[17,18] One HPLC method for the simultaneous determination of lansoprazole enantiomers and their metabolites has been reported; however, this method was only suitable for the analysis of *in vitro* microsomal samples and could not be applied to human plasma samples.[19] Therefore, we developed an HPLC method for the simultaneous quantitative determination of lansoprazole enantiomers and their metabolites, 5-hydroxylansoprazole enantiomers and lansoprazole sulfone, in human plasma.[20] Chromatographic separation for analytes

and (*S*)-omeprazole as an internal standard was achieved with a Chiral CD-Ph column (250 mm × 4.6 mm I.D., Shiseido, Tokyo, Japan) using a mobile phase of 0.5 *M* $NaClO_4$- acetonitrile-methanol (6: 3: 1, v/v). The analysis required only 100 μl of plasma and involved a solid-phase extraction with an Oasis HLB cartridge (Waters, Milford, MA, USA). The extraction recovery was high (>94.1%) and there was good selectivity. The lower limit of quantification of this assay was 10 ng/ml for each enantiomer of both lansoprazole and 5-hydroxylansoprazole, and 5 ng/ml for lansoprazole sulfone. The coefficient of variation for inter- and intra-day assays was less than 8.0% and accuracies were within 8.4% for all analytes (concentration range 10–4000 ng/ml). This method was suitable for the simultaneous monitoring of lansoprazole enantiomers and their metabolites in humans plasma.[20]

Analysis of Rabeprazole Enantiomers and Their Metabolites in Human Plasma An HPLC method for the simultaneous determination of rabeprazole enantiomers and their metabolites, which required a 1 ml plasma sample and had a quantification limit of 30 ng/ml for each compound, has been reported for dog plasma.[21] There have been no reports of a method for human plasma. Therefore, we developed an HPLC method for the simultaneous quantitative determination of rabeprazole enantiomers and their metabolites, rabeprazole-thioether and rabeprazole sulfone, in human plasma.[22] Analytes and the an internal standard, omeprazole-thioether, were separated using a mobile phase of 0.5 *M* $NaClO_4$-acetonitrile (6: 4, v/v) over a Chiral CD-Ph column. Analysis required 100 μl of plasma and involved solid-phase extraction with an Oasis HLB cartridge, which gave a high recovery (>91.8%) and good selectivity for all analytes. The lower limit of quantification was 5 ng/ml for each rabeprazole enantiomer and rabeprazole sulfone, and 10 ng/ml for rabeprazole-thioether. Inter- and intra-day coefficients of variation were less than 7.8% and accuracies were within 8.4% over the linear range for all analytes (concentration range 5–1000 ng/ml). This method was also applicable for the simultaneous monitoring of plasma concentrations of rabeprazole enantiomers and associated metabolites in human plasma.[22]

CLINICAL STUDIES IN HEALTHY SUBJECTS AND RENAL TRANSPLANT RECIPIENTS

Pharmacokinetic Profile of Lansoprazole Enantiomers in Healthy Subjects We evaluated the pharmacokinetics of lansoprazole enantiomers after a single oral administration of 60 mg lansoprazole to 18 healthy subjects, 6 each of homEMs, hetEMs and PMs.[23] The plasma concentrations of (*R*)-lansoprazole were markedly higher for all three CYP2C19 genotype groups compared to those of the corresponding (*S*)-enantiomer (Fig. 2). The relative area under the plasma concentration (AUC) ratios of (*R*)- and (*S*)-lansoprazole in the homEMs, hetEMs and PMs was 1: 1.5: 4.0 ($AUC_{0-\infty}$ values: 5009, 7300 and 20132 ng·h/ml), and 1: 1.8: 7.4 ($AUC_{0-\infty}$ values: 524, 967 and 3892 ng·h/ml), respectively. The mean maximum plasma concentration (C_{max}) of (*S*)-lansoprazole differed significantly among the homEMs, hetEMs and PMs (337, 528 and 1156 ng/ml, respectively), whereas there was no significant difference for the (*R*)-enantiomer (1957, 2196 and 2516 ng/ml, respectively) (Table 1). Thus, the magnitude of the contribution of CYP2C19 on (*S*)-lansoprazole was greater compared to that of the (*R*)-enantiomer. The *R*/*S* ratios for the AUC of lansoprazole in the homEMs, hetEMs and PMs was 12.7, 8.5 and 5.8, respectively, suggesting that CYP2C19 polymorphisms have a significant effect on the stereoselective disposition of lansoprazole.[23]

Pharmacokinetic Profile of Rabeprazole Enantimers in Healthy Subjects We examined the pharmacokinetics of rabeprazole enantiomers in relation to CYP2C19 genotype status by administering 20 mg of racemic rabeprazole to 24 healthy Japanese subjects, 8 each of CYP2C19 homEMs, hetEMs and PMs.[24] After a single oral dose of 20 mg of racemic rabeprazole, plasma concentrations of the rabeprazole enantiomers were measured. The $AUC_{0-\infty}$ of (*R*)-rabeprazole in the homEMs, hetEMs and PMs was 1.8-, 2.2- and 2.4-fold greater than those of (*S*)-rabeprazole, respectively (Table 1). The relative AUC ratios of (*R*)- and (*S*)-rabeprazole in the homEMs, hetEMs and PMs was 1: 1.1: 2.1 (514, 573 and 1068 ng·h/ml, respectively) and 1: 0.9: 1.5 (294, 260 and 445 ng·h/ml, respectively) (Table 1). The C_{max} of (*R*)-rabeprazole in the homEMs, hetEMs and PMs was 1.7-($p<0.05$), 1.9-($p<0.05$) and 1.8-($p<0.005$) fold higher, respectively, than those of the cor-

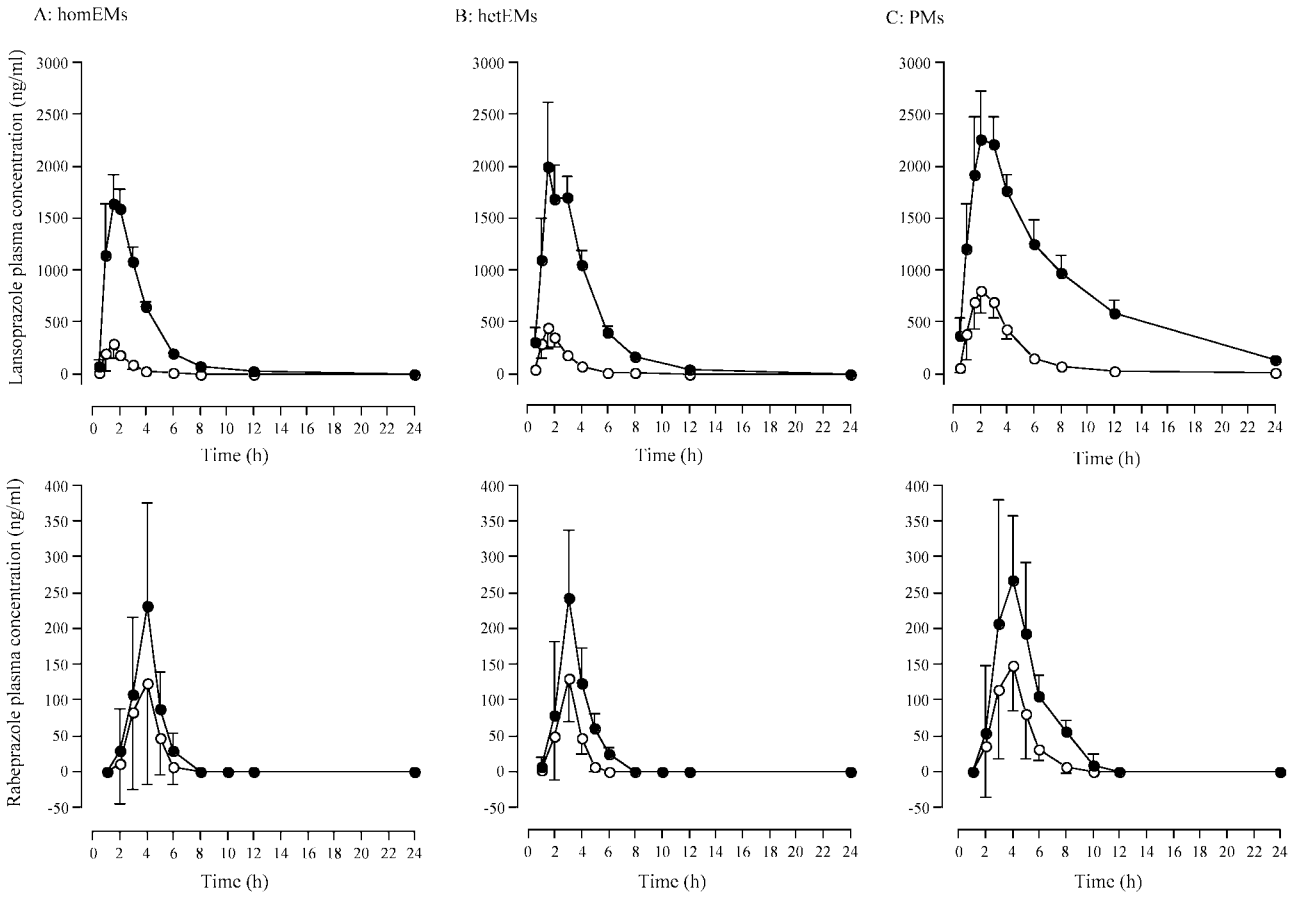

Fig. 2. Plasma Concentration-time Profiles of the (*R*)- (Solid Circles) and (*S*)-Enantiomers (Open Circles) of Lansoprazole (Upper Panel) and Rabeprazole (Lower Panel) in CYP2C19 Homozygous EMs (A), Heterozygous EMs (B) and PMs (C)

Subjects received a single oral dose of either 60 mg of racemic lansoprazole or 20 mg of racemic rabeprazole. The results are plasma concentration shown as the mean±S.D.

responding (*S*)-enantiomer. There was no difference between homEMs and PMs in the elimination half-life of (*S*)-rabeprazole, whereas the elimination half-life of (*R*)-rabeprazole was significantly longer in PMs than in homEMs (1.7 vs. 0.8 h, respectively, $p<0.0001$). The disposition of (*R*)-rabeprazole was influenced to a greater degree by CYP2C19 genetic polymorphisms than (*S*)-rabeprazole.[24] In *in vitro* studies, rabeprazole is reduced primarily through non-enzymatical methods to rabeprazole-thioether, which is then stereoselectively re-oxidized by CYP3A4 mainly to (*R*)-rabeprazole and is partially metabolized to desmethylrabeprazole-thioether by CYP2C19 (Fig. 1).[25] The difference in the enantioselective disposition of rabeprazole is determined by stereoselectivity in the CYP3A4-mediated metabolic conversion from rabeprazole-thioether to rabeprazole. Our findings show that the effect of CYP2C19 polymorphisms on the stereoselective disposition of rabeprazole is less than that of lansoprazole.[24]

Pharmacokinetic Profile of Lansoprazole and Rabeprazole Enantiomers in Renal Transplant Recipients Previously, no data was available concerning the enantioselective disposition of lansoprazole and rabeprazole in renal transplant recipients. Clinically, there is a need to precisely understand the pharmacokinetics of lansoprazole and rabeprazole with regard to tacrolimus management in transplant recipients. We investigated the comparison of enantioselective disposition between enantiomers of rabeprazole and lansoprazole in CYP2C19 EM renal transplant recipients.[26] In these patients, the PPIs are typically administered with tacrolimus, an immunosuppressive agent, in order to prevent gastric ulcer disease. Sixteen Japanese patients were randomly assigned after renal transplantation to receive repeated doses of tacrolimus and mycophenolate mofetil together with either 20 mg of racemic rabeprazole ($n=8$) or 30 mg of racemic lansoprazole ($n=8$) for 28

Table 1. Pharmacokinetic Parameters of (*R*)- and (*S*)-Enantiomer of Lansoprazole and Rabeprazole in Renal Transplant Recipients and Healthy Subjects

Genotype	Renal transplant recipients	Healthy subjects		
	EMs	homEMs	hetEMs	PMs
	28 days repeated dose	Single dose		
Lansoprazole	30 mg		60 mg	
(*R*)-enantiomer				
C_{max} (ng/ml)	954±552	1957±413	2196±405	2516±357
T_{max} (h)	3.9±1.5	1.9±0.6	2.3±0.8	2.4±0.9
$T_{1/2}$ (h)	2.3±1.0	1.3±0.3***	1.5±0.2***	5.0±1.0
AUC (ng·h/ml)	4787±3454	5009±919***	7300±1008***	20132±3570
(*S*)-enantiomer				
C_{max} (ng/ml)	167±137###	337±135**###	528±166*###	1156±253##
T_{max} (h)	3.3±1.3	1.7±0.7	1.8±0.7	1.9±0.6
$T_{1/2}$ (h)	1.2±0.6##	0.6±0.1***###	0.7±0.2***###	1.6±0.5###
AUC (ng·h/ml)	451±354##	524±189***###	967±224**###	3892±992###
R/*S*				
AUC	12.0±4.6	12.7±4.5	8.5±1.9	5.6±1.5
Rabeprazole	20 mg		20 mg	
(*R*)-enantiomer				
C_{max} (ng/ml)	186±40	257±116	279±76	330±97
T_{max} (h)	4.3±1.9	3.6±0.7	2.9±0.4	3.5±0.9
$T_{1/2}$ (h)	2.1±0.5	0.8±0.2***	0.9±0.2***	1.7±0.4
AUC (ng·h/ml)	759±485	514±258***	573±75***	1068±212
(*S*)-enantiomer				
C_{max} (ng/ml)	200±92	145±50#	153±51#	201±44##
T_{max} (h)	4.3±1.9	3.5±0.8	2.8±0.5	3.5±0.8
$T_{1/2}$ (h)	1.3±0.9#	0.8±0.3	0.7±0.2	1.0±0.1###
AUC (ng·h/ml)	617±505	294±154#	260±49##	445±88###
R/*S*				
AUC	1.2±0.8	1.8±0.4*	2.2±0.3	2.4±0.4

* $p<0.05$, ** $p<0.005$, *** $p<0.001$ vs. PMs. # $p<0.05$, ## $p<0.005$, ### $p<0.001$ vs. (*R*)-enantiomer.

days. The mean $AUC_{0-\infty}$ of (*R*)-lansoprazole in CYP2C19 EM renal transplant recipients was 12.0-fold greater than that of the (*S*)-enantiomer ($p<0.005$) (Table 1). This AUC ratio is nearly the same as the ratios seen in CYP2C19 EM healthy subjects.[17,23] However, the t_{max} value of (*R*)- and (*S*)-lansoprazole in renal transplant recipients (3.9 and 3.3 h, respectively) is much longer than t_{max} values in healthy subjects (1.9 and 1.7 h, respectively) who do not consume any food for 12 h prior to experiments.[23] These data suggest that the absorption of lansoprazole is greatly affected by digestion, since lansoprazole is an enteric coated product.[27] Although food consumption delays the t_{max} value, no effect is observed for the half-life ($t_{1/2}$).

In contrast, the *R*/*S* ratios of 1.2 and 0.9 have been reported for the AUC and C_{max} of rabeprazole in CYP2C19 EM renal transplant recipients, respectively.[26] There was no difference in the C_{max} of renal transplant recipients between (*R*)- and (*S*)-rabeprazole (186 vs. 200 ng/ml, respectively) (Table 1). Although the enantioselective disposition of lansoprazole in renal transplant recipients is similar to that in CYP2C19 EM healthy subjects,[17,23] the enantioselective disposition of rabeprazole in renal transplant recipients differs from that in healthy subjects.[24] Further studies are necessary in order to examine the difference in absorption and first pass metabolism of rabeprazole enantiomers between renal transplant recipients and healthy subjects.

Effect of Clarithromycin and Fluvoxamine on the Pharmacokinetics of Lansoprazole Enantiomers

Effect of Clarithromycin on Lansoprazole Enantiomer Kinetics Clarithromycin is mainly metabo-

lized by CYP3A4 in the liver and is a potent inhibitor of CYP3A4 based on *in vitro* and *in vivo* studies.[28−30] Lansoprazole is also metabolized by CYP3A4 to lansoprazole sulfone.[6−8] A drug interaction is believed to occur when lansoprazole and clarithromycin are co-administered, resulting in an increase in the plasma concentration of lansoprazole. We examined the effect of clarithromycin on the enantioselective disposition of lansoprazole among three different CYP2C19 genotype groups in 18 healthy *H. pylori*-negative Japanese subjects, 6 homEMs, 6 hetEMs and 6 PMs.[31] After 400 mg clarithromycin or a matched placebo was given orally twice a day for 6 days, each subject received an oral dose of 60 mg of lansoprazole. Clarithromycin significantly increased the AUC for (*R*)- and (*S*)-lansoprazole in the homEMs by 185% and 215%, in the hetEMs by 180% and 247%, and in the PMs by 242% and 208%, respectively (Fig. 3). The $AUC_{0-\infty}$ of each lansoprazole enantiomer was approximately doubled by the addition of clarithromycin in each CYP2C19 genotype (180–247% of control) (Fig. 3). There was no significant difference in the extent of AUC increase by clarithromycin between (*R*)- and (*S*)-lansoprazole among the three different CYP2C19 genotypes, although in the EMs clarithromycin did increase the $AUC_{0-\infty}$ of (*S*)-lansoprazole compared to the (*R*)-enantiomer (Fig. 3). Clarithromycin also significantly prolonged the elimination half-lives of (*R*)- and (*S*)-lansoprazole by 51% and 49%, respectively ($p<0.01$) in the CYP2C19 PMs, but not in the CYP2C19 homEMs or hetEMs.[31]

The drug interactions between (*R*)- or (*S*)-lansoprazole and clarithromycin in CYP2C19 EMs occurs through inhibition of CYP3A4-catalyzed sulfoxidation primarily during the first pass, whereas in CYP2C19 PMs drug interactions occur through inhibition of the overall metabolism of lansoprazole.[31] It has also been reported that the CYP3A4-mediated first pass sulfoxidation of (*R*)- and (*S*)-lansoprazole is not influenced by grapefruit juice.[32] Grapefruit juice inhibits CYP3A4 in the intestine, but not in the liver, leading to reduced intestinal first pass metabolism and an increased oral bioavailability of drugs.[33,34] Lansoprazole is mainly metabolized to lansoprazole sulfone by hepatic CYP3A4, but not intestinal CYP3A4.[32]

Effect of Fluvoxamine on Lansoprazole Enantiomer Kinetics Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is a known potent CYP1A2 inhibitor and also inhibits CYP2C19.[35,36] In a control study (section 2), the magnitude of the contribution of CYP2C19 to (*S*)-lansoprazole was greater than that to the (*R*)-enantiomer.[23] Therefore, when lansoprazole is administered in the presence of fluvoxamine, a resultant increase in the plasma concentration of (*S*)-lansoprazole compared with that of the (*R*)-enantiomer can be assumed. Eighteen healthy sub-

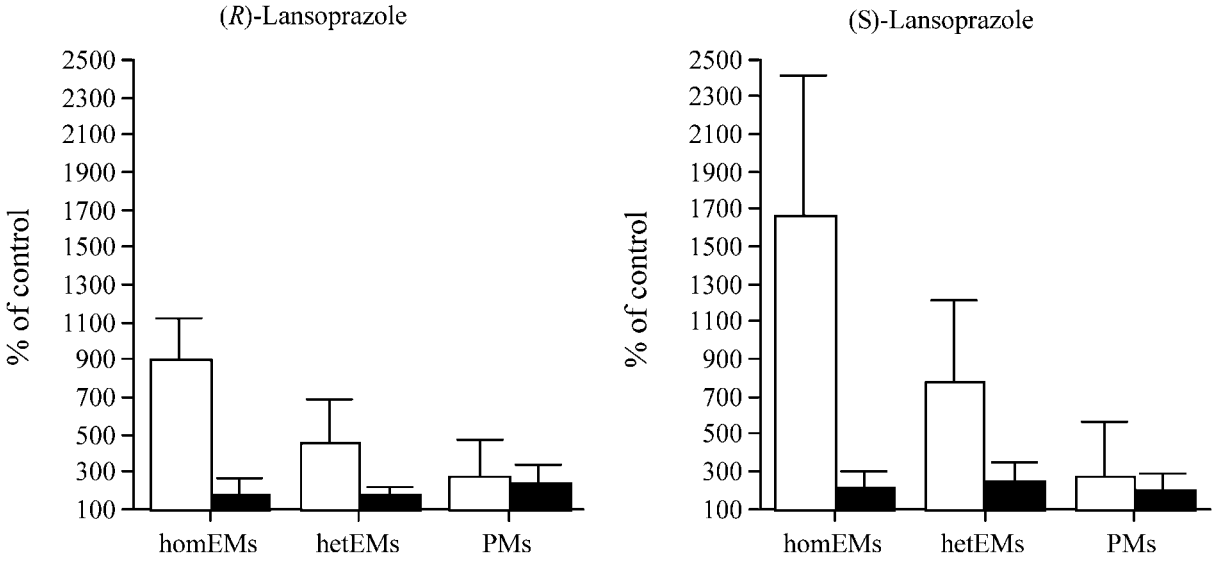

Fig. 3. The Change in $AUC_{0-\infty}$ of (*R*)- (Left) and (*S*)-Lansoprazole (Right) by Fluvoxamine (Open Bars) and Clarithromycin (Solid Bars) among the Three CYP2C19 Genotype Groups
Error bars indicate S.D.

jects, (6 homEMs, 6 hetEMs and 6 PMs) received placebo or 25 mg fluvoxamine twice daily for 6 days, then a single oral dose of 60 mg of racemic lansoprazole.[37] Fluvoxamine significantly increased the AUC for (*R*)- and (*S*)-lansoprazole in the homEMs by 903% and 1664%, in the hetEMs by 462% and 781%, respectively (Fig. 3). Thus, the drug interaction is more marked between (*S*)-lansoprazole and fluvoxamine than between (*R*)-lansoprazole and fluvoxamine. Consequently, the magnitude of the contribution of CYP2C19 to the metabolism of (*S*)-lansoprazole is much greater compared to that of the (*R*)-enantiomer. In extensive metabolizers, hepatic CYP2C19 plays an important role in the first pass metabolism and elimination of lansoprazole, particularly the (*S*)-enantiomer.[37]

CONCLUSION

The magnitude of contribution of each lansoprazole enantiomer for CYP2C19 was greater than that for CYP3A4. Furthermore, CYP2C19 had a greater influence on the disposition of (*S*)-lansoprazole than on the (*R*)-enantiomer. The *R*/*S* ratios for the AUC of lansoprazole for the homEMs, hetEMs and PMs were 12.7, 8.5 and 5.8, respectively. On the other hand, the degree of CYP2C19-mediated metabolism of (*R*)-rabeprazole was greater than in the (*S*)-enantiomer. The *R*/*S* ratios for the AUC of rabeprazole in homEMs, hetEMs, and PMs were 1.8, 2.2 and 2.4, respectively, suggesting that there was a lesser effect from CYP2C19 polymorphisms on the stereoselective disposition of rabeprazole compared to lansoprazole.

Although the clinical relevance of the effect of each enantiomer is not yet fully established, the pharmacological activities of these PPIs based on data obtained from *in vitro* studies is thought to be similar. Therefore, particularly in the case of lansoprazole, the use of the (*R*)-lansoprazole alone would be highly desirable for clinical application.

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