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RESEARCH PAPER

Hydroxylation of *R*(+)- and *S*(−)-Omeprazole after Racemic Dosing are Different among the CYP2C19 Genotypes

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ABSTRACT

Purpose To elucidate the stereoselective pharmacokinetics of omeprazole enantiomers and their metabolites after racemic IV dosing because there is little information about the stereoselective metabolism of omeprazole in *in vivo* study.

Methods Seventeen subjects were classified into three CYP2C19 groups based on their genotypes: homozygous extensive metabolizers (hmEMs; $n=5$), heterozygous EMs (htEMs; $n=7$) and poor metabolizers (PMs; $n=5$).

Results After single IV administration of racemic omeprazole (20 mg), the mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) of *R*(+)-omeprazole in PMs was significantly higher than that in hmEMs and htEMs, while that of *S*(−)-omeprazole was no significance among three genotypes because of a wide inter-individual variability. In addition, although the $AUC_{0-\infty}$ of *R*(+)-5-hydroxyomeprazole were determined among three genotypes, the that of *S*(−)-5-hydroxyomeprazole was undetectable in the hmEMs and barely detectable in the htEMs. Conversly, the $AUC_{0-\infty}$ of *S*(−)-5-hydroxyomeprazole was greater than that of *R*(+)-5-hydroxyomeprazole in the PMs.

Conclusions These data therefore suggest that, for EMs, the CYP2C19-mediated formation from *R*(+)-enantiomer is a 5-hydroxy-metabolite, while that from *S*(−)-enantiomer may be a minor metabolite. Thus, the *in vivo* disposition of *S*(−)- and *R*(+)-omeprazole after racemic dosing may be different among the CYP2C19 genotypes.

KEY WORDS CYP2C19 · *R*(+)-5-hydroxyomeprazole · *R*(+)-omeprazole · *S*(−)-5-hydroxyomeprazole · *S*(−)-omeprazole

ABBREVIATIONS

AUC	area under the plasma concentration-time curve
C_{max}	maximum plasma concentration
CYP	cytochrome P450
hmEMs	homozygous extensive metabolizers
HPLC	high-performance liquid chromatography
htEMs	heterozygous extensive metabolizers
IV	intravenous
ke	elimination rate constant
PMs	poor metabolizers
PO	oral administration
PPI	proton pump inhibitor
$t_{1/2}$	elimination half-life

INTRODUCTION

Omeprazole (5-methoxy-2-{[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl}-1H-benzimidazole) is a proton pump inhibitor (PPI) that inhibits gastric acid secretion by interacting with the (H^+/K^+)-ATPase, and it is widely used to treat various

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acid-related gastrointestinal disorders (1–3). Omeprazole is extensively metabolized to 5-hydroxyomeprazole and omeprazole sulfone. The formation of 5-hydroxyomeprazole is mainly mediated by CYP2C19, whereas the formation of omeprazole sulfone is mediated by CYP3A4 (Fig. 1) (4,5). The pharmacokinetics and pharmacodynamics of omeprazole significantly depend on the CYP2C19 genotype. The higher plasma concentrations of omeprazole in PMs have been shown to increase its effectiveness in anti-*H. pylori* therapy by higher gastric pH, and possibly in increasing the stability of antimicrobials in clinical situations (6). The AUC of oral omeprazole in the CYP2C19 PMs is 6- to 10-fold greater than that of the extensive metabolizers (EMs) (7–10).

Omeprazole has an asymmetric sulfur in its chemical structure and is therapeutically administered as a racemic mixture of *R*(+)-omeprazole and *S*(−)-omeprazole. An oral formation of the *S*(−)-enantiomer (esomeprazole) has been launched as the first single enantiomer PPI in Europe (2000) and USA (2001). *In vitro* studies using human liver microsomes have shown stereoselective metabolism of omeprazole, and although *R*(+)- and *S*(−)-omeprazole are subject to the same metabolic transformations (hydroxylation and sulfone formation), there are quantitative differences in their metabolic transformations. For *R*(+)-omeprazole, hydroxylation via CYP2C19 and sulfoxidation via CYP3A4 are responsible for 98 % and 2 % of its metabolic transformation, respectively, whereas these values are 73 % and 27 %, respectively, for *S*(−)-omeprazole (11). Additionally, two *in vivo* studies using a 20 mg oral dose of either *S*(−)-omeprazole or omeprazole have demonstrated that the AUC of *S*(−)-omeprazole is approximately 80 % higher than the racemic omeprazole (12). Additionally, for the CYP2C19 hmEMs, the AUC of *S*(−)-omeprazole has been shown to be 143 % and 43 % higher than that of *R*(+)-omeprazole and the racemic omeprazole, respectively (13). Furthermore, our recent study (14), which investigated the effects of different CYP2C19 genotypes on the metabolism of racemic omeprazole after a 40 mg oral dose, has shown that the AUC of *S*(−)-omeprazole is slightly greater than that of *R*(+)-omeprazole in EMs; in contrast, in PMs, the AUC of *R*(+)-omeprazole was significantly greater than that of *S*(−)-omeprazole. In addition, the $AUC_{0-\infty}$ of omeprazole sulfone, an achiral metabolite by CYP3A4, correlated with $AUC_{0-\infty}$ of omeprazole of CYP2C19 genotypes. These findings suggest that both CYP3A4 and 2C19 for omeprazole metabolism after PO dosing have affected the AUCs of omeprazole and its metabolite. Furthermore, it has been reported that the secondary metabolites of omeprazole are also determined by both CYP2C19 and CYP3A4 activities (5).

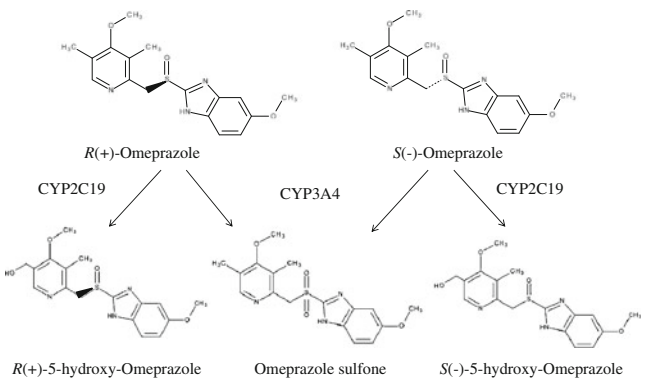

Fig. 1 Metabolic pathways of omeprazole enantiomers.

To date, although there are few *in vivo* pharmacokinetic studies (14,15) on the omeprazole enantiomers related to CYP2C19 genotypes after oral racemic omeprazole dosing, there is no information concerning when administrered intravenously. Therefore, the aim of this study was to elucidate the stereoselective disposition of omeprazole enantiomers and their metabolites in relation to the different CYP2C19 genotypes following a single IV dose of racemic omeprazole except for the influence of the metabolism in the small intestine after PO dosing.

MATERIALS AND METHODS

Subjects and Study Design

All of the subjects in this study participated in our previous study (16). The Ethics Committee of the Hirosaki University School of Medicine approved this study protocol, and written informed consent was obtained from each participant before any examinations. The mean (±SD) age and body weight of the volunteers were 28.6 (±7.0) years (range 21–44 years) and 63.0 (±15.1) kg (range 42–90 kg), respectively. After an overnight fast, 17 subjects (11 males and 6 females) were given 20 mg of omeparazole (Omepral® Injection 20, AstraZeneca Co., Osaka, Japan: Omepral® is racemic mixture of the (*S*)- and (*R*)-enantiomer, i.e. a 50/50 mixture of its enantiomers.) IV over 60 s. Blood samples were collected before the IV dose and 5 min and 0.5, 1, 2, 3, 4, 6, and 8 h after the IV dose. The volunteers did not take any medication or consume any fruit juices for at least 7 days before either of the study phases, and no meals or beverages were allowed until 4 h after omeprazole administration.

The subjects previously underwent a CYP2C19 genotyping test using a polymerase chain reaction-restriction fragment length polymorphism method with allele-specific primers to identify the CYP2C19 wild-type (*1) gene and the 2 mutated alleles, CYP2C19*2 (*2) in exon 5 and CYP2C19*3 (*3) in exon 4 (17); the subjects were classified into 1 of 3 genotype groups as follows: hmEMs (*1/*1, 5 subjects) htEMs (*1/*2 or *1/*3, 7 subjects) or PMs (*2/*2 or *2/*3, 5 subjects).

Analysis of the Omeprazole Enantiomers and Their Metabolites in the Plasma

The plasma concentrations of the omeprazole enantiomers and their metabolites were determined by the high-performance liquid chromatography (HPLC) method previously described by our laboratory (14). In brief, 10 μL of 50 μg/mL lansoprazole sulfone as an internal standard and 0.1 mL of 0.05 M disodium hydrogen phosphate were added to 1 mL of plasma. The tubes were vortexed for 5 s, and 4 mL of diethylether-dichloromethane (60:40, *v/v*) was added as the extraction solvent. After 10 min of vortexing, the mixture was centrifuged at 3500 × g for 10 min at 4 °C (himac CF16RX, Hitachi, Tokyo, Japan), and the organic phase was evaporated *in vacuo* at 50 °C until dry (EYELA MG-2200, Tokyo Rikakikai, Tokyo, Japan). The residue was dissolved with 30 μL of methanol and 100 μL of 0.05 M disodium hydrogen phosphate buffer (pH 9.3), and a 30 μL aliquot was injected onto the column. The column-switching HPLC system consisted of two Shimadzu (Kyoto, Japan) LC-10ADVP high-pressure pumps (for eluent A and B), a Shimadzu CTO-10AVP column oven, and a Shimadzu Workstation LC solution chromatography integrator, a Shimadzu SPD-10AV and a Shimadzu SIL-10ADVP (500 μL injection volume). A TSK BSA-ODS/S precolumn was used for sample clean up (column I: 10 mm×4.6 mm i.d., particle size 5 μm; Tosho, Tokyo, Japan), and a Shiseido CD-ph chiral column (column II: 150 mm×4.6 mm i.d., particle size 5 μm; Shiseido Co. Limit., Tokyo, Japan) was used. The mobile phases consisted of a phosphate buffer (pH 6.4, 0.01 M) and acetonitrile (97:3, *v/v*) (eluent A) for clean-up and phosphate buffer (pH 5.0, 0.05 M) and methanol (45:55, *v/v*) (eluent B) for separation. The flow rates of eluents A and B were 1.2 and 0.4 mL/min, respectively. The temperature of columns I and II was 40 °C. Peaks were detected at a wavelength of 302 nm. The lower limit of quantification for this assay was 5 ng/mL for all of the analytes. The calibration graphs were obtained in a concentration range of 5–1000 ng/mL for *R*(+)- and *S*(−)-omeprazole, 5–500 ng/mL for *R*(+)- and *S*(−)-5-hydroxyomeprazole and 5–1000 ng/mL for omeprazole sulfone. The coefficient of validation for the inter- and intra-day assays was <9.6 %, and the accuracy was within <9.3 % for the all of the analytes.

Pharmacokinetic Data Analyses

The maximum plasma concentration (C_{max}) was determined directly from the observed data. The elimination rate constant (ke) for omeplazole was obtained by a linear regression analysis using at least 3 sampling points in the terminal log-linear declining phase to the last measurable concentration. The apparent elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by the ke. The AUC from time zero to the last sampling time ($AUC_{0\text{-last}}$) was calculated using the linear trapezoidal rule. The AUC from 0 to infinity ($AUC_{0\text{-}\infty}$) was calculated by $AUC_{0\text{-last}} + C_{last}/ke$, where C_{last} is the last detectable plasma drug concentration. The total clearance (CL) was calculated by dose/$AUC_{0\text{-}\infty}$. The *R/S* AUC ratio was calculated as ($AUC_{0\text{-}\infty}$ of *R*(+)-omeprazole)/($AUC_{0\text{-}\infty}$ of *S*(−)-omeprazole).

Statistical Analyses

The pharmacokinetic parameters among the three different genotypes were compared using a one-way ANOVA followed by Scheffe's test. A paired t-test was used to compare the pharmacokinetic parameters of the *R*(+)- and *S*(−)-enantiomers. All of the data were analyzed with the statistical program StatView 5.0 (Abacus Concept, Berkeley, Chicago, USA). A value of $P<0.05$ was considered statistically significant.

RESULTS

The mean plasma concentration-time curves of *R*(+)-omeprazole were higher than those of *S*(−)-omeprazole in the PMs, whereas there were no differences in the plasma concentrations-time curves between *R*(+)-omeprazole and *S*(−)-omeprazole in the EMs (hmEMs and htEMs) (Fig. 2a). The $AUC_{0\text{-}\infty}$ of *R*(+)-omeprazole was significantly greater in the PMs than in the EMs. However, for *S*(−)-omeprazole, there were no significant differences in the pharmacokinetic parameters between the htEMs and the PMs. Furthermore, the relative $AUC_{0\text{-}\infty}$ ratios for *R*(+)- and *S*(−)-omeprazole in the hmEMs, the htEMs and the PMs were 1:2.6:14.2 and 1:1.8:4.6, respectively. The *R/S* ratios of the $AUC_{0\text{-}\infty for}$ omeprazole were 0.8, 1.2 and 2.4 for the hmEMs, the htEMs and the PMs, respectively, and the *R/S* ratio of the PMs was significantly higher than that of the hmEMs and the htEMs (Table I).

Although the plasma concentration-time curves were not different between the *R*(+)- and *S*(−)-omeprazole in hmEMs and the htEMs, the plasma concentration of *R*(+)-5-hydroxyomeprazole was significantly higher than *S*(−)-5-hydroxyomeprazole in hmEMs and htEMs (Fig. 2b). However, *S*(−)-5-hydroxyomeprazole was not always detectable in the hmEMs and the htEMs (Fig. 2b and Table II). The Cmax and $AUC_{0\text{-}\infty}$ of *S*(−)-5-hydroxyomeprazole in the PMs were significantly higher than those in the htEMs, while the C_{max} of *R*(+)-5-hydroxyomeprazole in the PMs were significantly lower than that in the hmEMs and the htEMs.

In addition, the mean plasma concentration-time curves and $AUC_{0\text{-}\infty}$of omeprazole sulfone were significantly higher in the PMs that in the hmEMs and htEMs (Fig. 3 and Table III), and the relative $AUC_{0\text{-}\infty}$ ratio of omeprazole sulfone in the hmEMs, the htEMs and the PMs was 1:1:5.3, respectively (Table III).

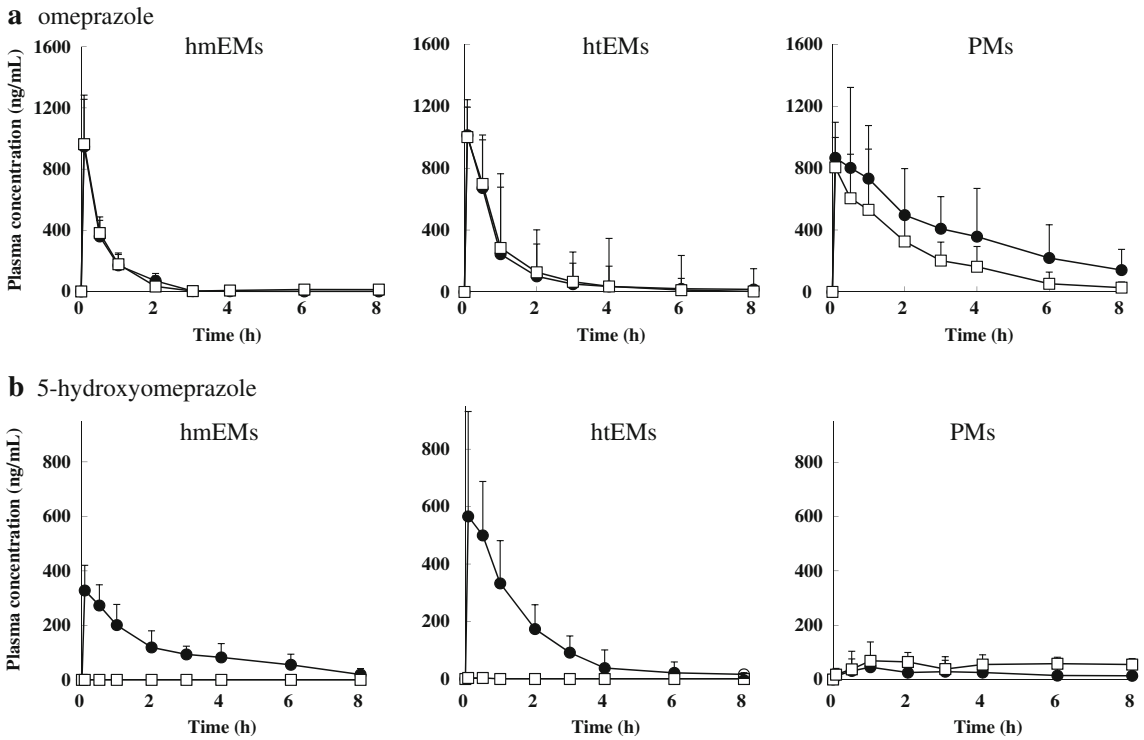

Fig. 2 (**a**): Plasma concentration-time curves (mean + S.D) of *R*(+)-enantiomers (solid circles) and *S*(−)-enantiomers (open squares) of omeprazole, (**b**): *R*(+)-enantiomers (solid circles) and *S*(−)-enantiomers (open squares) of 5-hydroxyomeprazole in homozygous EMs, heterozygous EMs and PMs after IV administration.

DISCUSSION

We investigated the pharmacokinetics of the omeprazole enantiomers in different CYP2C19 genotypes after a single IV dose of racemic omeprazole. This is the first report of the enantioselective disposition of omeprazole and its metabolites in three CYP2C19 genotypes after IV dosing of racemic omeprazole. In a recent report that investigated the stereoselective

Table I Pharmacokinetic Parameters of *R*(+)-Omeprazole and *S*(−)-Omeprazole

	hmEMs		htEMs		PMs	
	n = 5		n = 7		n = 5	
	R(+)	*S*(-)	*R*(+)	*S*(-)	*R*(+)	*S*(-)
C_{max} (ng/mL)	947 ± 320	964 ± 309	1132 ± 615	1110 ± 606	1027 ± 425	1009 ± 431
$AUC_{0-\infty}$ (ng h/mL)	293 ± 136	390 ± 148	761 ± 362	715 ± 423	4167 ± 3203$^{*,\#}$	1808 ± 1299*
					§	
$t_{1/2}$ (h)	0.4 ± 0.3	0.3 ± 0.1	2.1 ± 2.2	1.7 ± 3.1	1.4 ± 0.3	1.2 ± 0.6
CL (mL/min)	81 ± 36	59 ± 27	27 ± 8	34 ± 22	12 ± 9$^{***,\#\#}$	22 ± 12*
	§					
R/S $AUC_{0-\infty}$ ratio	0.8 ± 0.2		1.1 ± 0.3		2.4 ± 0.8$^{**,\#}$	

Data are shown as mean ± S.D. values

The *R/S* ratios of AUC; (AUC0-∞ *R*(+)-omeprazole)/ (AUC0-∞ *S*(−)-omeprazole)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with the hmEMs group

# $P < 0.05$, ## $P < 0.01$, compared with the htEMs group

§$P < 0.05$, between *R*(+)-omeprazole and *S*(−)-omeprazole

Table II Pharmacokinetic Parameters of *R*(+)-Hydroxyomeprazole and *S*(−)-5-Hydroxyomeprazole

	hmEMs		htEMs		PMs	
	n = 5		n = 7		n = 5	
	R(+)	S(-)	*R*(+)	S(-)	*R*(+)	S(-)
C_{max} (ng/mL)	356 ± 78	N.D.	625 ± 356	3.3 ± 6.8	63 ± 65**, ##	54 ± 59###
			§ §			
$AUC_{0-\infty}$ (ng h/mL)	969 ± 447	N.D.	897 ± 706	16.5 ± 51.7	312 ± 505	694 ± 752#
			§ § §			
$t_{1/2}$ (h)	1.6 ± 1.3	N.D.	0.5 ± 0.3	0.6 ± 1.7	1.7 ± 2.9	0.9 ± 0.8

Data are shown as mean ± S.D. values

**$P < 0.01$, compared with the hmEMs group

# $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$, compared with the htEMs group

§$P < 0.05$, §§$P < 0.01$, §§§$P < 0.001$, between *R*(+)-hydroxyomeprazole and *S*(−)-hydroxyomeprazole

pharmacokinetics after the PO administration of omeprazole (14), the relative $AUC_{0-\infty}$ ratios of *R*(+)- and *S*(−)-omeprazole (*R*/*S*) were 0.8 for the hmEMs, 0.9 for the htEMs, and 2.0 for the PMs; these findings are in agreement with previous results observed by Tybring *et al.* (15). In the present study, after an IV dose of omeprazole, the relative *R*/*S* $AUC_{0-\infty}$ ratios were 0.8 for the hmEMs, 1.1 for the htEMs, and 2.4 for the PMs. Because the results from both PO and IV administration of omeprazole are closely similar, therefore, it implies that omeprazole stereoselective disposition would be primary influenced by the CYP2C19-mediated metabolism in the liver.

Interestingly, when single isomers of omeprazole were orally administered separately (13), the AUC of *S*(−)-omeprazole was more than two times greater than that of *R*(+)-omeprazole on days 1 and 5. In the present study, the AUCs of *R*(+)- and *S*(−)-omeprazole were nearly identical in the hmEMs and the htEMs. In contrast, the AUC of *R*(+)-omeprazole was more than two times greater than that of *S*(−)-omeprazole in the CYP2C19 PMs. However, these differing results might be explained by reports that *R*(+)-omeprazole inhibits the CYP2C19-dependent metabolism of S(−)-omeprazole in human liver microsomes, whereas *S*(−)-omeprazole was not shown to inhibit *R*(+)-omeprazole metabolism (18). In addition, when *S*(−)-omeprazole was inhibited by *R*(+)-omeprazole, CYP3A4 became increasingly important for *S*(−)-omeprazole metabolism and less important for *R*(+)-omeprazole metabolism. Therefore, following the administration of racemate, the plasma concentrations of *S*(−)-omeprazole might be similar to those of *R*(+)-omeprazole due to contribution of the CYP3A4-mediateted pathway: These findings suggest that CYP3A4 might compensate for reduced CYP2C19-mediated metabolism of omeprazole in CYP2C19 PMs.

An *in vitro* study by Äbelö *et al.* (11) has indicated that hydroxylation via CYP2C19 is responsible for 98 % of the total intrinsic clearance of *R*(+)-omeprazole, whereas it is only responsible for approximately 70 % of the total intrinsic clearance of *S*(−)-omeprazole. In contrast, CYP3A4-mediated sulfone

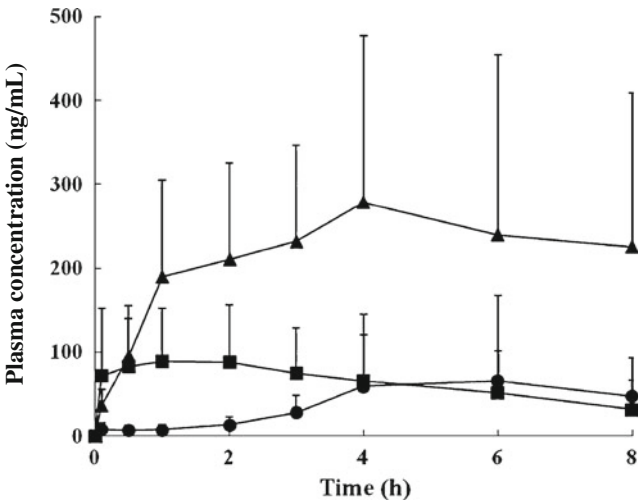

Fig. 3 Plasma concentration-time curves (mean + S.D) of omeprazole sulfone in homozygous EMs (closed circles), heterozygous EMs (closed squares) and PMs (closed triangles) after IV administration.

Table III Pharmacokinetic Parameters of Omeprazole Sulfone

	hmEMs *n*=5	htEMs *n*=7	PMs *n*=5
C_{max} (ng/mL)	82 ± 121	95 ± 77	285 ± 197
$AUC_{0-\infty}$ (ng h/mL)	864 ± 850	873 ± 764	4592 ± 3730*, #
$t_{1/2}$ (h)	4.9 ± 6.8	0.9 ± 1.0	4.3 ± 2.4*, #

Data are shown as mean ± S.D. values

*$P < 0.05$, compared with the hmEMs group

# $P < 0.05$, compared with the htEMs group

formation is responsible for only 2 % of the total intrinsic clearance of *R*(+)-omeprazole; however, it is responsible for almost 30 % of the total intrinsic clearance of *S*(−)-omeprazole. In the present study, the relative $AUC_{0-\infty}$ ratios of *R*(+)- and *S*(−)-omeprazole in the hmEMs, the htEMs and the PMs were 1:2.6:14.2 and 1:1.8:4.6, respectively. These results therefore suggest that our *in vivo* data reflect previous *in vitro* data, and significant differences in the $AUC_{0-\infty}$ ratios among the CYP2C19 genotypes may affect *R*(+)-omeprazole to a greater extent than *S*(−)-omeprazole. Hence, since the clinical effects of *R*(+)-omeprazole and *S*(−)-omeprazole are almost similar (19), our *in vivo* results show that the wide inter-individual differences of the pharmacokinetics and the pharmacodynamics after racemic PO and IV administration might be primarily due to the CYP2C19-mediated hydroxylation of *R*(+)-omeprazole.

Similar to our previous result after PO dosing (14), in the present IV dosing study, $AUC_{0-\infty}$ of *R*(+)-5-hydroxyomeprazol is the lowest in the PMs among the CYP2C19 genotypes and this result has correlated with the lack of CYP2C19 activity. While, *S*(−)-5-hydroxyomeprazole, the CYP2C19-mediated formation from *S*(+)-enantiomer, was undetectable in the hmEMs and barely detectable in the htEMs. However, a previous *in vitro* study has been shown that *S*(−)-5-hydroxyomeprazole accounts for 27 % of the CYP2C19-mediated intrinsic clearance (20). This discrepancy of our *in vivo* results may also be due to omeprazole enantiomer/enantiomer interactions (18) by which *R*(+)-omeprazole inhibits the CYP2C19-mediated metabolism of *S*(−)-omeprazole. In addition, although we previously detected racemic 5-hydroxyomeprazole in the hmEMs and the htEMs after racemic dosing (16), there was no significance in the AUC of racemic 5-hydroxyomeprazole. Accordingly, this shows that a racemic 5-hydroxy-metabolite after omeprazole dosing was likely due to majorly *R*(+)5-hydroxyomeprazole. A prior *in vitro* study have been reported that the CYP2C19-mediated major metabolite of *S*(−)-omeprazole is primary *S*(−)5-*O*-desmethylomeprazole (46 % for the intrinsic clearance) (20). Hence, our present study to determine the hydroxylation of omeprazole enantiomers has a limitation because we did not detect *S*(−)5-*O*-desmethylomeprazole, and then additional *in vivo* studies are necessary to examine the CYP2C19-mediated 5-*O*-desmethylation pathway from *S*(−)-omeprazole.

Moreover, two *in vitro* and *in vivo* studies have indicated that CYP3A4 primarily replaces CYP2C19 for 5-hydroxyomeprazole formation in the CYP2C19 PMs (21,22). In addition, the previously mentioned *in vitro* data (11) suggest that CYP3A4 has a higher affinity for *S*(−)-omeprazole (30 % of its intrinsic clearance) than for *R*(+)-omeprazole (2 % of its intrinsic clearance); thus, *S*(−)-5-hydroxyomeprazole was expected to have a higher $AUC_{0-\infty}$ in the PMs who lack CYP2C19 activity than in the hmEMs or the htEMs. Furthermore, it is worth noting that the $AUC_{0-\infty}$ of *S*(−)-5-hydroxyomeprazole tended be higher than that of *R*(+)-5-hydroxyomeprazole in the PMs; however, this difference was not significant.

The main omeprazole metabolite generated by CYP3A4 is omeprazole sulfone, which is an achiral metabolite of omeprazole (4,5,11). Previous studies have reported that the secondary metabolism of omeprazole is performed by CYP2C19 and CYP3A4 (5). Notably, 5-hydroxyomeprazole is metabolized to 5-hydroxyomeprazole sulfone by CYP3A4, and omeprazole sulfone is metabolized to 5-hydroxyomeprazole sulfone by CYP2C19 (5). In the present study, the $AUC_{0-\infty}$ of omeprazole sulfone in the PMs was significantly greater than that of hmEMs and htEMs. These data were in agreement with our previous PO studies (14,16). These results therefore suggest that because omeprazole sulfone was not metabolized to 5-hydroxyomeprazole sulfone in the PMs, the $AUC_{0-\infty}$ of omeprazole sulfone in the PMs may be the greatest among CYP2C19 genotypes.

In conclusion, the present study indicates that the plasma concentrations and degree of CYP2C19-mediated metabolism of *R*(+)-omeprazole are greater than those of *S*(−)-omeprazole. The *R*/*S* ratios for the AUC of omeprazole in the hmEMs, the htEMs, and the PMs were 0.8, 1.1 and 2.4, respectively. These data suggest that there is a lesser effect of CYP2C19 polymorphisms on the disposition of *S*(−)-omeprazole compared with *R*(+)-omeprazole. In addition, the *in vivo* disposition of *S*(−)- and *R*(+)-omeprazole after racemic dosing may be different among the CYP2C19 genotypes.

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