Correlation Between *R/S* Enantiomer Ratio of Lansoprazole and CYP2C19 Activity After Single Oral and Enteral Administration

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ABSTRACT The purpose of this study was to investigate whether CYP2C19 activity can be estimated from plasma concentrations of lansoprazole enantiomers 4 h (C_{4h}) after single administration *by* oral and enteral routes. Sixty-nine subjects, 22 homozygous extensive metabolizers (homEMs), 32 heterozygous EMs (hetEMs), and 15 poor metabolizers (PMs), participated in the study. After a single oral or enteral dose of racemic lansoprazole (30 mg), plasma concentrations of lansoprazole enantiomers were measured 4 h postdose. The *R/S* ratio of lansoprazole at 4 h differed significantly among the three groups ($P < 0.0001$) regardless of the administration route. The *R/S* ratio of lansoprazole in CYP2C19 PMs ranged from 3.0 to 13.7, whereas in homEMs and hetEMs the ratio ranged from 8.6 to 90 and 2.1 to 122, respectively. The relationship between (*S*)-lansoprazole concentration and *R/S* ratio of lansoprazole at C_{4h} is given by the following formula: $\log_{10}$ [*R/S* ratio] = 2.2 – 0.64 × $\log_{10}$ [C_{4h} of (*S*)-lansoprazole] ($r = 0.867$, $P < 0.0001$). Thus, phenotyping CYP2C19 using the *R/S* enantiomer ratio of lansoprazole seems unlikely. However, to obtain a pharmacological effect similar to that in CYP2C19 PMs, we can presume that lansoprazole has a sufficient effect in the patient with an *R/S* enantiomer ratio at 4 h ≤ 13.70 and (*S*)-lansoprazole concentration at 4 h ≥ 50 ng/ml. *Chirality 22:635–640, 2010.*

KEY WORDS: lansoprazole; enantiomer; CYP2C19

INTRODUCTION

Lansoprazole is a proton pump inhibitor (PPI) that inhibits gastric acid secretion through an interaction with (H^+/K^+)-ATPase in gastric parietal cells.[1] Gastroesophageal reflux and heartburn caused by esophagectomy are reported in 20–65% of esophageal cancer patients.[2–6] A PPI is often administered to prevent development of gastric acid reflux-related symptoms in patients after esophagectomy.[5–7] After esophagectomy, it is difficult for patients to ingest a PPI. Often, intestinal or gastric fistulae are constructed for enteral feeding as well as PPI administration until normal ingestion is possible. Until now, lansoprazole pharmacokinetics after placement in an intestinal fistula has not been published. For patients with difficulty in ingestion, an intraoral enteric coated preparation of lansoprazole is widely used, rather than omeprazole and rabeprazole, which cannot be broken up as only coated tablets are available.

Lansoprazole is metabolized to 5-hydroxylansoprazole and lansoprazole sulfone mainly by CYP2C19 and CYP3A4, respectively.[8,9] This hydroxylation pathway is the main metabolic route of lansoprazole; and is strongly influenced by *CYP2C19* polymorphisms.[10,11] Lansoprazole has an asymmetric sulfur in its chemical structure. Plasma concentrations of (*R*)-lansoprazole were consistently higher than those of the (*S*)-enantiomer in both extensive metabolizers (EMs) and poor metabolizers (PMs) of CYP2C19.[12,13] Such different pharmacokinetics of lansoprazole enantiomers are assumed to be due to enantioselective protein binding and metabolism.[12–14] In the previous study, differences between the plasma concentration of (*R*)- and (*S*)-enantiomers of lansoprazole were greatest 4 h after oral administration.[15] On the other hand, in our previous study, r^2 for the predictive formulae for the area under the plasma concentration–time curve (AUC) of racemic lansoprazole, which included the *CYP2C19* genotype and plasma concentrations of (*R*)- and (*S*)-lansoprazole at 3 (C_{3h}) and 4 h (C_{4h}) after oral administration was 0.897 and 0.835, respectively.[16] C_{3h} or C_{4h} of lansoprazole enantiomers are useful time points to estimate AUC of racemic lansoprazole.[16] Generally, many blood collection timepoints are required to calculate accurate AUC values. It is clinically important that AUC predictions are calculated

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TABLE 1. Clinical characteristics of subjects

	Oral administration				Enternal administration			
	Healthy subjects				Patients after esophagectomy			
Study group	homEMs	hetEMs	PMs	*P*-value	homEMs	hetEMs	PMs	*P*-value
Patients (female/male)	11 (5/6)	11 (6/5)	8 (4/4)		11 (0/11)	21 (3/18)	7 (3/4)	
Gastroesophageal reflux disease					1	1	0	
Age (yr)	31.4 ± 11.8	30.6 ± 9.0	30.0 ± 11.0	0.931	63.8 ± 7.8	65.7 ± 5.4	62.7 ± 8.7	0.511
Weight (kg)	56.1 ± 11.8	55.5 ± 8.8	61.0 ± 15.7	0.863	62.9 ± 8.0	53.1 ± 8.9	55.8 ± 12.1	0.031
Aspartate transaminase (IU/l)					30.5 ± 10.7	27.4 ± 10.2	21.3 ± 6.6	0.146
Alanine transaminase (IU/l)					47.3 ± 15.6	37.9 ± 19.8	27.3 ± 14.3	0.086
Total bilirubin (mg/dl)					0.6 ± 0.6	0.4 ± 0.2	0.3 ± 0.0	0.082
Serum albumin (g/dl)					3.6 ± 0.4	3.6 ± 0.3	3.6 ± 0.2	0.878
Serum creatinine (mg/dl)					0.7 ± 0.1	0.7 ± 0.2	0.6 ± 0.1	0.279

Data were mean values and SD, except for the patient number.
homEMs, homozygous extensive metabolizers; hetEMs, heterozygous EMs; PMs, poor metabolizers.

from limited patient samples. Therefore, we hypothesized that estimating CYP2C19 activity is possible from plasma concentrations of lansoprazole enantiomers 4 h after lansoprazole administration.

The purpose of this study was to investigate whether human CYP2C19 activity can be estimated by using plasma concentrations of lansoprazole enantiomers 4 h after a single oral or enteral dose.

PATIENTS AND METHODS

Patients and Protocols

Thirty healthy Japanese subjects [11 homozygous (hom) EMs, 11 heterozygous (het) EMs, and eight PMs] participated in this study. All subjects fasted for 10 h before administration of 30 mg lansoprazole and during the test period. Thirty-nine patients [11 homozygous EMs (homEMs), 21 heterozygous EMs (hetEMs), and seven PMs] who underwent esophagectomy at Akita University Hospital without neo-adjuvant treatment for esophageal cancer between April 2007 and October 2008 were enrolled in this study after confirmed histological diagnosis of esophageal cancer. These patients received right transthoracic esophagectomy and dissection of two (mediastinal and abdominal) or three (bilateral neck, mediastinal, and abdominal) lymph node fields. Our operative procedure did not change during the study period, and standard reconstruction was done using the gastric tube via the posterior mediastinal route. Esophagectomy patient characteristics are listed in Table 1. None of the 39 patients received a drug or food that affected CYP3A, CYP2C19, and P-glycoprotein function. All subjects received a 30 mg single dose of lansoprazole orally or enterally (Takepron®, Takeda) with a glass of tap water at 08:00. Venous blood samples were taken for the determination of plasma concentrations of lansoprazole enantiomers 4 h later. Blood samples were subjected to centrifugation at 3000*g* immediately after collection and stored at −80°C until analyzed. The study protocol was approved by the Ethics Committee of Akita University School of Medicine, and all subjects gave their written informed consent before participating.

CYP2C19 Genotyping

DNA was extracted from a peripheral blood sample using a QIAamp blood kit (Qiagen, Hilden, Germany) and was stored at −80°C until analysis. Genotyping procedures used 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.[17] Genotype confirmation by sequencing was not performed. However, the frequency for the different loci analyzed was at the Hardy-Weinberg equilibrium for Asian population.[18] The *CYP2C19* genotype analysis revealed 5 different patterns: **1/*1* in 22, **1/*2* in 23, **1/*3* in 9, **2/*2* in 10, and **2/*3* in 5. These were divided into three groups, homEMs (**1/*1*, $n = 22$), hetEMs (**1/*2* and **1/*3*, $n = 32$), and PMs (**2/*2* and **2/*3*, $n = 15$).

Analysis of Lansoprazole Enantiomers in Plasma

The plasma concentration of lansoprazole enantiomers was determined according to the HPLC method of Miura et al.[19] The lower limit of quantification for this assay was 10 ng/ml for each lansoprazole enantiomer. The coefficient of variation of the inter- and intra-day assays was <8.0%, and the accuracy was within 8.4% for the two enantiomer analytes (concentration range of 10–4000 ng/ml).[19]

Statistical Analysis

One-way ANOVA and the Fisher exact test were used for comparisons between three *CYP2C19* genotypes and clinical profiles such as age, body weight and gender in healthy subjects and esophageal cancer patients. Pharmacokinetic parameters such as C_{4h} of (*R*)- and (*S*)-lansoprazole and the *R/S* ratio for the three genotype groups were compared using the Kruskal–Wallis test followed by the Mann–Whitney test. The pharmacokinetic parameters of lansoprazole enantiomers in each *CYP2C19* genotype for healthy subjects and esophageal cancer patients were compared using the Mann–Whitney test. The relationships between C_{4h} of (*S*)-lansoprazole and the *R/S* ratio were evaluated using a distribution map. $P < 0.05$ were considered statistically significant. The Stat View program (SAS

TABLE 2. (*R*)- and (*S*)-Lansoprazole plasma concentration 4 h after administration in three CYP2C19 genotypes

			homEMs $n = 11$ (OA), $n = 11$ (EA)	hetEMs $n = 11$ (OA), $n = 21$ (EA)	*PMs* $n = 8$ (OA), $n = 7$ (EA)	*P*-value[§]
(*R*)-Lansoprazole	OA		492.2 ± 358.0	697.9 ± 334.1	954.3 ± 248.1$^{\#\#}$	0.006229
		Range	(162–1314)	(267–1545)	(538–1425)	
	EA		603.5 ± 283.2	664.4 ± 383.3	1000.8 ± 313.6$^{\#}$	0.022794
		Range	(226–1056)	(167–1899)	(650–1583)	
	OA + EA		547.8 ± 320.1	675.9 ± 363.6	976.0 ± 271.1$^{\#\#}$	0.000236
(*S*)-Lansoprazole	OA		33.3 ± 45.9	69.2 ± 55.9	251.6 ± 91.8$^{\#\#\#}$	0.000362
		Range	(1.8–152)	(3.8–188)	(47–339)	
	EA		26.5 ± 17.2	58.9 ± 60.3	129.2 ± 74.8$^{*,\#\#\#}$	0.002785
		Range	(5.7–55)	(3.0–210)	(61–250)	
	OA + EA		29.9 ± 34.0	62.4 ± 58.1$^{\#}$	194.5 ± 103.0$^{\#\#\#}$	0.000001
R/S ratio	OA		36.8 ± 27.0	19.2 ± 18.5	4.6 ± 2.8$^{\#\#\#}$	0.004522
		Range	(8.6–90)	(2.1–70)	(3.0–11.5)	
	EA		30.0 ± 15.7	23.3 ± 25.5	9.2 ± 3.3$^{***,\#\#\#}$	0.000992
		Range	(10.5–55.5)	(5.5–122)	(4.8–13.7)	
	OA + EA		33.4 ± 21.9	21.9 ± 23.1$^{\#}$	6.7 ± 3.8$^{\#\#\#}$	0.000002
		Median	30.19	16.09	4.88	
		First-tertiary quart	13.04–43.40	10.02–23.39	3.57–9.92	

The values are shown as the mean ± SD (ng/ml).
[§]*P*: compared among three CYP2C19 genotypes (Kruskal–Wallis test).
$^{\#}P < 0.05$, $^{\#\#}P < 0.005$, $^{\#\#\#}P < 0.0005$: compared with homEMs (Mann–Whitney test).
$^{*}P < 0.05$, $^{***}P < 0.0005$: compared with oral administration (Mann−Whitney test).homEMs, homozygous extensive metabolizers; hetEMs, heterozygous extensive metabolizers; PMs, poor metabolizers; OA, oral administration; EA, enteral administration.

Institute, Cary, NC, version 5.0) was used for all statistical analyses.

RESULTS

There were no differences among the three *CYP2C19* genotype groups in parameters such as age and body weight in healthy subjects (Table 1). In addition, after esophagectomy, there were no differences between the three *CYP2C19* genotype groups in terms of age and biochemical data (aspartate transaminase, alanine transaminase, bilirubin, albumin, and serum creatinine) (Table 1). There was no significant difference between the body weight of orally and enterally administered subject groups ($P = 0.935$); however, the mean age of the enterally administered subjects was significantly higher than that of the orally administered subjects (64.6 vs. 30.7 yr, respectively) ($P < 0.001$). The subjects included one CYP2C19 homEM and one hetEM patient with gastric acid reflux.

In both administration types, C_{4h} of (*S*)-lansoprazole was more intensely affected by a *CYP2C19* polymorphism than that of the (*R*)-enantiomer (Table 2). The mean C_{4h} of (*S*)-lansoprazole after enteral administration differed significantly among the three *CYP2C19* genotypes ($P = 0.002785$). The mean *R/S* ratio of lansoprazole at C_{4h} for the enterally administered CYP2C19 PMs was 9.2 and was significantly lower compared with the homEMs ($P < 0.0005$) (Table 2).

The mean C_{4h} of (*R*)- and (*S*)-lansoprazole after oral administration differed significantly among the three *CYP2C19* genotypes ($P = 0.006229$ and 0.000362, respectively). The mean *R/S* ratio of lansoprazole at C_{4h} *in* the orally administered CYP2C19 PMs was 4.6 and was significantly lower than the enterally administered PMs ($P < 0.0005$) (Table 2). However, in CYP2C19 homEMs and hetEMs there were no significant differences in the C_{4h} of (*R*)- and (*S*)-lansoprazole and the *R/S* ratio of lansoprazole at C_{4h} between orally and enterally administered subject groups.

The *R/S* ratio of lansoprazole at C_{4h} differed significantly among the three groups ($P = 0.000002$) without considering route of administration (oral or enteral), with a relative ratio of 5.0 in the homEMs, 3.3 in the hetEMs, and 1.0 in the PMs (Table 2). The relative C_{4h} of (*S*)-lansoprazole in homEMs, hetEMs, and PMs was 1.0, 2.0, and 6.5 ($P = 0.000001$).

The *R/S* ratio of lansoprazole in CYP2C19 PMs ranged from 3.0 to 13.7, whereas that in homEMs and hetEMs was from 8.6 to 90 and 2.1 to 122, respectively (Table 2). The *R/S* ratio range for lansoprazole in CYP2C19 EMs was large (Table 2 and Fig. 1). The relationship between (*S*)-lansoprazole concentration and *R/S* enantiomer ratio of lansoprazole at the C_{4h} sampling point is shown in the following formula: $\log_{10}$ [*R/S* ratio of lansoprazole] = 2.2 – 0.64 × $\log_{10}$ [C_{4h} of (*S*)-lansoprazole] ($r = 0.867$, $P < 0.0001$).

The median *R/S* ratio of lansoprazole in CYP2C19 homEMs, hetEMs, and PMs was 30.19 (13.04–43.40), 16.09 (10.02–23.39), and 4.88 (3.57–9.92), respectively. In CYP2C19 PMs, there were no outlier values (see Fig. 2).

DISCUSSION

We investigated whether human CYP2C19 activity can be estimated using C_{4h} of lansoprazole enantiomers when

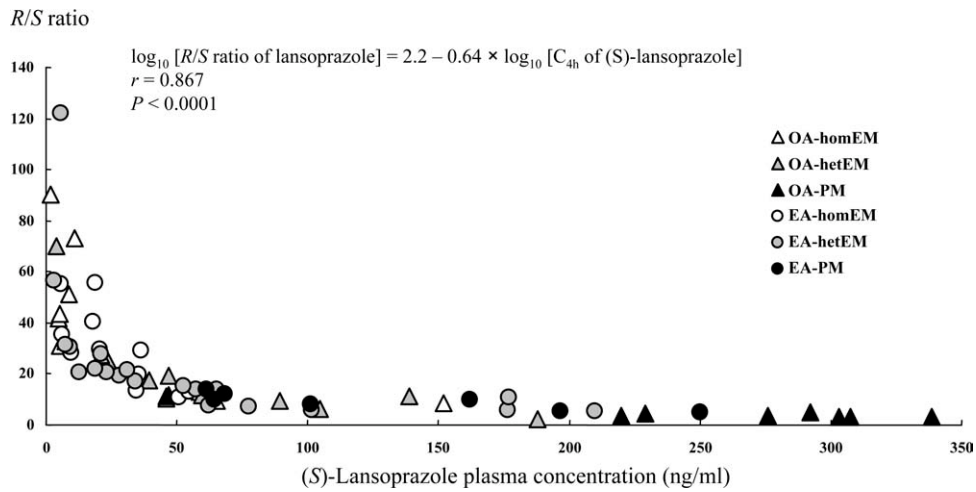

Fig. 1. Correlation between *R/S* enantiomer ratio at C_{4h} of lansoprazole and (*S*)-lansoprazole plasma concentration at C_{4h} in all data sets ($n = 69$). OA, oral administration; EA, enteral administration; homEM, homozygous extensive metabolizer; hetEM, heterozygous EM; PM, poor metabolizer.

oral and enteral administration is used. Regardless of the route of administration, the *R/S*-enantiomer ratio at C_{4h} of lansoprazole and the C_{4h} value of (*S*)-lansoprazole correlated with the *CYP2C19* genotype. The *R/S* ratio at C_{4h} of lansoprazole and C_{4h} value of (*S*)-lansoprazole in CYP2C19 homEMs were statistically different from those in hetEMs and PMs ($P = 0.015$ and 0.013 for hetEMs, respectively, and each $P < 0.0001$ for PMs). In addition, the *R/S* ratio at C_{4h} of lansoprazole and C_{4h} value of (*S*)-lansoprazole had relative ratios of 1.0:0.66:0.20 ($P < 0.0001$) and 1.0:2.0:6.5 ($P < 0.0001$), respectively, in CYP2C19 homEMs, hetEMs, and PMs. Thus, although there was a significant difference in the *R/S* enantiomer ratio of lansoprazole between *CYP2C19* genotypes, there is an overlapping range between *R/S* enantiomer ratio in CYP2C19 EMs and PMs (2.1–122 and 3.0–13.7, respectively). Therefore, CYP2C19 phenotyping seems unlikely using this *R/S* enantiomer index. If we perform CYP2C19 phenotyping using the *R/S* enantiomer index, the sensitivity and specificity for CYP2C19 PMs using a cut-off *R/S* enantiomer ratio of 10.00 were 73.3% and 81.5%, respectively.

In CYP2C19 homEMs and hetEMs, there was no significant difference in C_{4h} of (*R*)- and (*S*)-lansoprazole and the *R/S* ratio of lansoprazole at C_{4h} between orally and enterally administered subject groups. This finding showed that lansoprazole pharmacokinetics in CYP2C19 EM patients was similar after oral and enteral administration. On the other hand, although the *R/S* ratio of lansoprazole in CYP2C19 PMs had a relatively narrow range (3.0–13.7), there were significant differences in mean *R/S* ratio at C_{4h} of lansoprazole and mean C_{4h} of (*S*)-lansoprazole between the orally and enterally administered PMs (4.6 and 9.2, respectively, $P < 0.0005$, and 251.6 and 126.2 ng/ml, respectively, $P < 0.05$). In some subjects with CYP2C19 PMs, the main metabolic pathway of lansoprazole is shifted from CYP2C19 to CYP3A4. For these groups, CYP3A4 is an important lansoprazole-metabolizing enzyme. On the other hand, several studies have shown reductions in liver volume, hepatic blood flow and CYP3A activity with aging.[20–24] In our present study, the mean age of the enterally administered subjects was significantly higher than that of the orally administered subjects (64.6 vs. 30.7 yr, respectively). Therefore, plasma concentrations of both enantiomers of lansoprazole should increase. However, C_{4h} of (*S*)-lansoprazole, but not (*R*)-lansoprazole, tended to be lower in the enterally administered subjects than in the orally administered subjects. Unfortunately, we

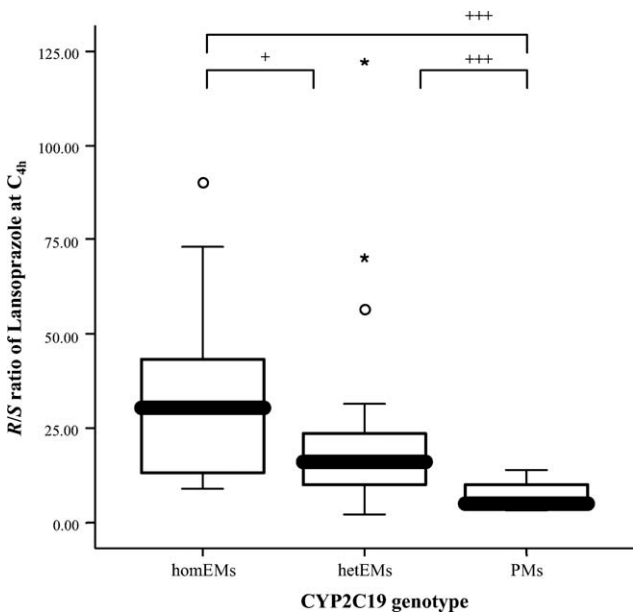

Fig. 2. Comparison of the distribution of *R/S* enantiomer ratio at C_{4h} of lansoprazole between three different CYP2C19 genotype groups. Graphical analysis used the SPSS box and whiskers plot. The box spans data between the two quartiles (IQR), with the median represented as a bold horizontal line. The ends of the whiskers (vertical lines) represent the smallest and largest values that are not outliers. Outliers (circles) are values between 1.5 IQRs and 3 IQRs from the end of a box. Values more than three IQRs from the end of a box are defined as extreme (asterisk). $^{+}P < 0.05$, $^{+++}P < 0.0001$. homEM, homozygous extensive metabolizer; hetEM, heterozygous EM; PM, poor metabolizer.

cannot find the cause that can explain this phenomenon fully. In enterally administered CYP2C19 PMs, the interaction between two lansoprazole enantiomers may occur in the intestine, resulting in a change of the pharmacokinetic profile of (*S*)-lansoprazole. In any event, without considering administration route and aging, the mean *R/S* ratio at C_{4h} of lansoprazole and C_{4h} of (*S*)-lansoprazole in the CYP2C19 PMs were statistically different from those in homEMs and hetEMs.

Without considering lansoprazole administration route, the *R/S* enantiomer ratio at C_{4h} of lansoprazole correlated well with the C_{4h} value of (*S*)-lansoprazole as the fractional expression described below: $\log_{10}$ [*R/S* ratio of lansoprazole] = 2.2 – 0.64 × $\log_{10}$ [C_{4h} of (*S*)-lansoprazole] (r = 0.867, $P < 0.0001$). The magnitude of contribution of CYP2C19 for each lansoprazole enantiomer is greater than that for CYP3A4. Lansoprazole is metabolized by hepatic CYP3A4, but not intestinal CYP3A4.[25] The contribution of CYP3A4 to the metabolism of (*S*)-lansoprazole is greater than to the (*R*)-enantiomer.[9,26] In addition, the magnitude of the contribution of CYP2C19 to (*S*)-lansoprazole metabolism is greater than towards the (*R*)-enantiomer.[12,13,27] This finding has led to the development of dexlansoprazole, the (*R*)-enantiomer of lansoprazole.[28]

We were unable to completely distinguish *CYP2C19* genotypes with the *R/S* enantiomer ratio of lansoprazole. *CYP2C19* genetic polymorphisms may not completely explain CYP2C19 activity in an individual.[29] The *R/S* enantiomer ratio of 13.70 and (*S*)-lansoprazole at C_{4h} of 50 ng/ml were border values for CYP2C19 PMs. The range of *R/S* ratio of lansoprazole in CYP2C19 EMs was large. In the CYP2C19 EM patients, individual differences in clinical pharmacological effect are great, and present a clinical problem. Cure rates for gastroesophageal reflux disease depend significantly on *CYP2C19* genotype. Furuta et al.[30] report that cure rates for gastroesophageal reflux disease with a daily dose of lansoprazole (30 mg) for 8 wk in the CYP2C19 homEMs, hetEMs, and PMs are 45.8%, 67.9%, and 84.6%, respectively. In addition, Sugimoto et al.[31] report that eradication rates of *Helicobacter pylori* by lansoprazole-based triple therapy in CYP2C19 PMs is 100%. In the present study, there were two CYP2C19 EM patients with gastric acid reflux, but no CYP2C19 PM patients. Lansoprazole pharmacokinetics are similar upon single and repetitive administration.[32] To obtain the same high pharmacological effect as CYP2C19 PMs, we can presume that lansoprazole has a sufficient pharmacological effect in the patient with an *R/S* enantiomer ratio $\leq$13.70 and (*S*)-lansoprazole at $C_{4h} \geq 50$ ng/ml.

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. Schmidt CE, Bestmann B, Küchler T, Schmid A, Kremer B. Quality of life associated with surgery for esophageal cancer: differences between collar and intrathoracic anastomoses. World J Surg 2004;28:355–360.
3. McLarty AJ, Deschamps C, Trastek VF, Allen MS, Pairolero PC, Harmsen WS. Esophageal resection for cancer of the esophagus: long-term function and quality of life. Ann Thorac Surg 1997;63:1568–1572.
4. Gutschow C, Collard JM, Romagnoli R, Salizzoni M, Hölscher A. Denervated stomach as an esophageal substitute recovers intraluminal acidity with time. Ann Surg 2001;233:509–514.
5. Yuasa N, Sasaki E, Ikeyama T, Miyake H, Nimura Y. Acid and duodenogastroesophageal reflux after esophagectomy with gastric tube reconstruction. Am J Gastroenterol 2005;100:1021–1027.
6. Shibuya S, Fukudo S, Shineha R, Miyazaki S, Miyata G, Sugawara K, Mori T, Tanabe S, Tonotsuka N, Satomi S. High incidence of reflux esophagitis observed by routine endoscopic examination after gastric pull-up esophagectomy. World J Surg 2003;27:580–583.
7. Okuyama M, Motoyama S, Maruyama M, Sasaki K, Sato Y, Ogawa J. Proton pump inhibitors relieve and prevent symptoms related to gastric acidity after esophagectomy. World J Surg 2008;32:246–254.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. Niioka T, Miura M, Uno T, Yasui-Furukori N, Hayakari M, Tateishi T, Suzuki T. Estimation of the area under the concentration–time curve of racemic lansoprazole by using limited plasma concentration of lansoprazole enantiomers. Eur J Clin Pharmacol 2008;64:503–509.
17. 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.
18. 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.
19. Miura M, Tada H, Suzuki T. Simultaneous determination of lansoprazole enantiomers and their metabolites in plasma by liquid chromatography with solid-phase extraction. Chromatogr B Analyt Technol Biomed Life Sci 2004;804:389–395.
20. Marchesini G, Bua V, Brunori A, Bianchi G, Pisi P, Fabbri A, Zoli M, Pisi E. Galactose elimination capacity and liver volume in ageing man. Hepatology 1988;8:1079–1083.
21. Woodhouse KW, Wynne HA. Age-related changes in liver size and hepatic blood flow. The influence on drug metabolism in the elderly. Clin Pharmacokinet 1988;15:287–294.
22. Wynne HA, Cope E, Mutch E, Rawlins MD, Woodhouse KW, James OFW. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 1989;9:297–301.

23. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 1997;61:331–339.
24. Ginsberg G, Hattis D, Russ A, Sonawane B. Pharmacokinetic and pharmacodynamic factors that can affect sensitivity to neurotoxic sequelae in elderly individuals. Environ Health Perspect 2005;113:1243–1249.
25. Miura M, Kagaya H, Tada H, Uno T, Yasui-Furukori N, Tateishi T, Suzuki T. Intestinal CYP3A4 is not involved in the enantioselective disposition of lansoprazole. Xenobiotica 2006;36:95–102.
26. Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Effect of clarithromycin on the enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes. Chirality 2005;17:338–344.
27. 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;60:61–68.
28. Vakily M, Lee RD, Wu J, Gunawardhana L, Mulford D. Drug interaction studies with dexlansoprazole modified release (TAK-390MR), a proton pump inhibitor with a dual delayed-release formulation : results of four randomized, double-blind, crossover, placebo-controlled, single-centre studies. Clin Drug Investig 2009;29:35–50.
29. 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.
30. Furuta T, Shirai N, Watanabe F, Honda S, Takeuchi K, Iida T, Sato Y, Kajimura M, Futami H, Takayanagi S, Yamada M, Ohashi K, Ishizaki T, Hanai H. Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. Clin Pharmacol Ther 2002;72:453–460.
31. Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, Ishizaki T, Hishida A. Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. Helicobacter 2007;12:317–323.
32. Miura M. Enantioselective disposition of lansoprazole and rabeprazole in human plasma. Yakugaku Zasshi 2006;126:395–402.