CYP2C19 Genotype and Pharmacokinetics of Three Proton Pump Inhibitors in Healthy Subjects

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Purpose. To predict the *CYP2C19* genotype-dependence in anti-*Helicobacter pylori* (*H. pylori*) therapy when lansoprazole or rabeprazole was used instead of omeprazole as a proton pump inhibitor (PPI).

Methods. A comparative pharmacokinetic study with each PPI was designed as an open, randomized, and crossover study of 18 Japanese healthy volunteers who were classified into the homozygous, heterozygous extensive metabolizer and the poor metabolizer based on the *CYP2C19* genotype determined by PCR-RFLP method. Each subject received a single oral dose of 20 mg omeprazole, 30 mg lansoprazole, or 20 mg sodium rabeprazole, with at least 1 week washout period between treatments. Plasma concentrations of PPIs and their metabolites were monitored until 12 h after medication.

Results. Pharmacokinetic profiles of omeprazole and lansoprazole were well correlated with the *CYP2C19* genotype. The heterozygous extensive metabolizer was slightly different from the homozygote, but there was no statistically significant difference. The *CYP2C19* genotype dependence found for lansoprazole was not obvious compared with omeprazole. As for rabeprazole, the pharmacokinetic profile was independent of the *CYP2C19* genotype.

Conclusions. *CYP2C19* genotype dependence will be found in the anti-*H. pylori* therapy even when lansoprazole is used as the PPI.

KEY WORDS: *CYP2C19* genotype; pharmacokinetics; proton pump inhibitor; omeprazole; lansoprazole; rabeprazole.

INTRODUCTION

Proton pump inhibitors (PPIs) are superior to H_2-receptor antagonists as acid inhibitory agents and are used in the treatment of upper gastrointestinal diseases such as peptic ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome (1). Recently, *Helicobacter pylori* (*H. pylori*) was demonstrated to possibly cause peptic ulcer (2,3) and gastric cancer (4,5), and triple therapy with PPI, amoxicillin, and clarithromycin/metronidazole is now recommended because of the high eradication rate (greater than 80%) (6). There still remains the incomplete eradication in the therapy, even though considerable dosage of antimicrobials are used. Three PPIs—omeprazole, lansoprazole, and sodium rabeprazole—are now commercially used in Japan. They are structurally similar benzimidazole derivatives, and *in vitro* human liver microsomal studies have demonstrated that cytochrome P450 2C19 (CYP2C19) is responsible for 5-hydroxylation of omeprazole and lansoprazole and demethylation of rabeprazole, and CYP3A4 is for sulfoxidation of the three PPIs (7–10).

CYP2C19, often referred to the S-mephenytoin 4′-hydroxylase, shows genetically determined polymorphism, which is expected to affect the pharmacokinetics of these PPIs, and the subsequent efficacy and toxicity in anti-*H. pylori* therapy. The pharmacokinetic profiles of omeprazole and lansoprazole have been found to correlate with the S-mephenytoin 4′-hydroxylator phenotype (11–16). The *CYP2C19* gene is located on chromosome 10p, and in addition to the wild-type allele *CYP2C19*1,* two mutant alleles *CYP2C19*2* and *CYP2C19*3* were recently found possibly responsible for genetically deficient metabolic activity (17–19). The *CYP2C19* genotype is well correlated with the pharmacokinetics of omeprazole (20,21) and the eradication of *H. pylori* after anti-*H. pylori* therapy using omeprazole (22,23). In these studies, there was no manifested conclusion concerning the classification of the subjects based on the *CYP2C19* genotype. The subjects could be reasonably classified into three groups consisting of the homozygous of *CYP2C19*1,* the heterozygous of *CYP2C19*1,* and the combination of mutant alleles, because the metabolic activity from *CYP2C19*2* and *CYP2C19*3* was almost perfectly deficient. However, the heterozygous *CYP2C19*1* is sometimes included with the homozygous *CYP2C19*1* as an extensive metabolizer without any rational evidence. The aims of the present study were 1) to predict the *CYP2C19* genotype-dependence in anti-*H. pylori* therapy when lansoprazole or rabeprazole was used instead of omeprazole, and 2) to elucidate the necessity to discriminate the homozygous *CYP2C19*1* and its heterozygote in the anti-*H. pylori* therapy using PPI. A comparative pharmacokinetic study with omeprazole, lansoprazole, and rabeprazole was designed as an open, randomized, and crossover study of Japanese healthy volunteers who were classified into the homozygous of wild-type *CYP2C19*1,* the heterozygous of *CYP2C19*1,* and the combination of mutant alleles.

MATERIALS AND METHODS

Chemicals

Omeprazole and its two primary metabolites, 5-hydroxyomeprazole and omeprazole sulfone, were obtained from AstraZeneca Ltd. (Osaka, Japan). Lansoprazole and its two primary metabolites, 5-hydroxylansoprazole and lansoprazole sulfone, were obtained from Takeda Pharmaceutical

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ABBREVIATIONS: CYP, cytochrome P450; *H. pylori, Helicobacter pylori;* PPI, proton pump inhibitor; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HPLC, high performance liquid chromatography; C_{max}, maximum plasma concentration; AUC, area under the plasma concentration-time curve from 0 to infinity; $t_{1/2}$, elimination half-life.

Co. (Osaka, Japan). Sodium rabeprazole and its two primary metabolites, thioether rabeprazole and rabeprazole sulfone, were obtained from Eisai Co. (Tokyo, Japan). All other chemicals were of reagent grade and obtained commercially.

Subjects and Study Protocol

CYP2C19 genotype was determined by the PCR-RFLP method (22,23). From 90 Japanese healthy volunteers, 18 selected subjects who agreed to participate in the following study were classified into three groups by the *CYP2C19* genotype; that is, the homozygous extensive metabolizers (n = 6; *CYP2C19*1/CYP2C19*1*), the heterozygous extensive metabolizers (n = 6; *CYP2C19*1/CYP2C19*2, CYP2C19*1/CYP2C19*3*), and the poor metabolizers (n = 6; *CYP2C19*2/CYP2C19*2, CYP2C19*2/CYP2C19*3, CYP2C19*3/CYP2C19*3*). The demographics were very similar among the three groups (Table I). None of the subjects had hepatic or renal dysfunction or had taken any medication, including alcohol and over-the-counter drugs, for at least 1 week before and during the study. Written informed consent was obtained from all subjects before the study commenced. The protocol was approved by the Institutional Review Board of Kobe University School of Medicine in advance.

Each subject received a single oral dose of 20 mg omeprazole (Omepral® tablet, AstraZeneca Ltd.), 30 mg lansoprazole (Takepron® capsule, Takeda Pharmaceutical Co.), or 20 mg sodium rabeprazole (Pariet® tablet, Eisai Co.) as the respective enteric-coated formulation with 100 ml water at 9:00 a.m. in a crossover manner, with at least 1 week washout period between treatment periods. Each drug was taken after at least a 10 h fasting, and a lunch was served 3 h after drug ingestion. Venous blood samples were collected prior to and at 1, 2, 3, 4, 6, and 12 h after medication. The plasma samples separated after centrifugation at 1500 × g for 10 min were stored frozen at –20°C until analyzed. It was confirmed that there was no alteration in the concentrations of any PPIs or their metabolites during storage.

HPLC Assay

The HPLC system consisted of an LC-10AT pump, a SIL-10A auto injector, a SPD-10A detector, a CTO-10A column oven (at 40°C), a SCL-10A system controller, and a C-R7A chromatopack (Shimadzu Co., Kyoto, Japan) and was used for the measurement of plasma concentrations of all PPIs and their primary metabolites.

Plasma concentrations of omeprazole and its two primary metabolites, 5-hydroxyomeprazole and omeprazole sulfone, were measured according to the method reported by Kobayashi *et al.* with slight modification concerning the extraction from the serum sample (24). Briefly, 100 μl of 0.1 mg phenacetin/ml methanol (internal standard) and 2 ml of diethyl ether-dichloromethane (7:3, v/v) were added to 0.5 ml of each plasma. They were extracted twice by shaking for 10 min, and the mixture was centrifuged at 1500 × g for 10 min. Then, 0.5 ml of propylene glycol was added to the supernatant, and the solvent was evaporated under a nitrogen stream at 40°C. Plasma concentrations of lansoprazole and its two primary metabolites, 5-hydroxylansoprazole and lansoprazole sulfone, were followed by the previously described HPLC method (25,26). Plasma concentrations of rabeprazole and its two primary metabolites, thioether rabeprazole and rabeprazole sulfone, were also measured according to the HPLC method by Nakai et al (27).

Pharmacokinetic Analysis

The maximum plasma concentrations (C_{max}) were obtained graphically. The area under the plasma concentration-time curve of each PPI and its primary metabolites was calculated using the linear trapezoidal rule from 0 to infinity (AUC). The first-order elimination rate constant (K) was calculated by the linear least-squares regression analysis of the respective terminal log-linear portion of plasma concentration-time profile. It is noted that this linear portion is determined visually, and the calculated value of K depended on the sampling schedule. The elimination half-life ($t_{1/2}$) was calculated as 0.693/K.

According to rational pharmacokinetic notation, the AUC of PPI metabolites depends on the parent PPI, and the AUC of PPI metabolites was corrected by dividing by that of the parent PPI to consider the metabolic processes more appropriately.

Statistical Analysis

The values are expressed as the mean value ± SE. The statistical differences in pharmacokinetic findings among the three groups were evaluated using one-way analysis of variance with a Scheffe-type multiple comparison test. P values less than 0.05 were considered significant.

Table I. *CYP2C19* Genotype and Characteristics of Healthy Subjects

	Homozygous extensive metabolizers (n = 6)	Heterozygous extensive metabolizers (n = 6)	Poor metabolizers (n = 6)
CYP2C19 genotype	*CYP2C19*1/CYP2C19*1* (n = 6)	*CYP2C19*1/CYP2C19*2* (n = 4) *CYP2C19*1/CYP2C19*3* (n = 2)	*CYP2C19*2/CYP2C19*2* (n = 2) *CYP2C19*2/CYP2C19*3* (n = 3) *CYP2C19*3/CYP2C19*3* (n = 1)
Male:Female ratio	5:1	5:1	5:1
Age (years)	26.0 ± 2.6	26.8 ± 3.1	25.8 ± 3.1
Weight (kg)	60.2 ± 6.3	58.5 ± 7.1	59.7 ± 5.9

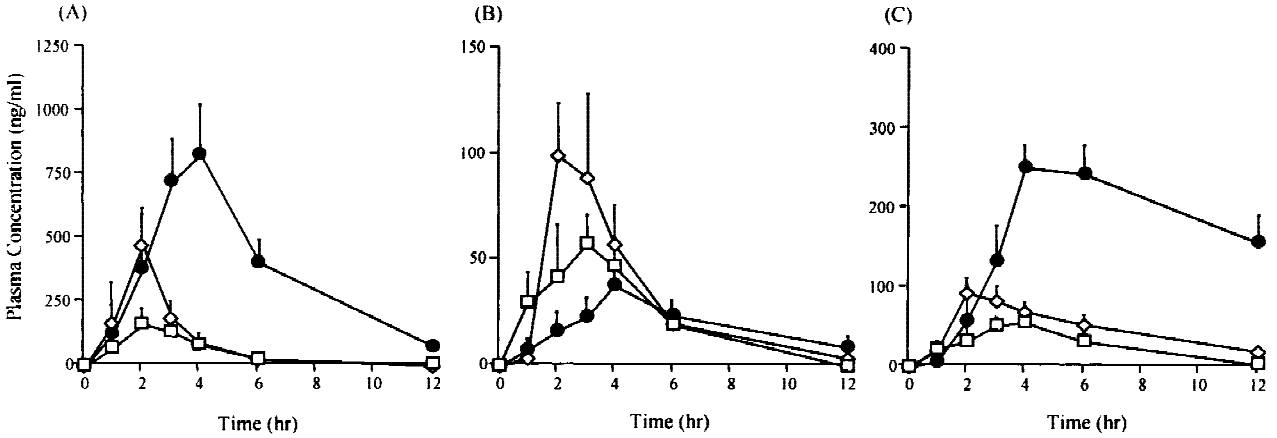

Fig. 1. Plasma concentrations of omeprazole (A), 5-hydroxyomeprazole (B), and omeprazole sulfone (C) after a single oral dosing of 20 mg omeprazole in the homozygous extensive metabolizers (□), heterozygous extensive metabolizers (◇), and poor metabolizers (●) classified by *CYP2C19* genotype. Each point represents the mean ± SE (n = 6).

RESULTS

Omeprazole

Figure 1 shows the plasma concentration-time curves of omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone after 20 mg omeprazole administration in the homozygous extensive metabolizers, the heterozygous extensive metabolizers, and the poor metabolizers, which were classified by the *CYP2C19* genotype. Plasma concentrations of omeprazole and omeprazole sulfone in poor metabolizers were much higher than those in homozygous or heterozygous extensive metabolizers, whereas 5-hydroxyomeprazole concentrations in poor metabolizers were relatively lower. Table II lists the pharmacokinetic parameters. The AUC of omeprazole in poor metabolizers was 7.4- and 4.3-fold higher than that in homozygous and heterozygous extensive metabolizers, respectively. The AUC of omeprazole sulfone was also higher in poor metabolizers, whereas there was no difference in the AUC of 5-hydroxyomeprazole among the three groups. When the AUC of 5-hydroxyomeprazole or omeprazole sulfone was corrected by that of the parent omeprazole, a significant difference was shown in 5-hydroxyomeprazole, but disappeared in omeprazole sulfone. The values of C_{max} also suggested differences among the three groups similarly to the AUC without significance. The maximum concentration of omeprazole and 5-hydroxyomeprazole was achieved at 2.2–3.8 h after administration for all groups. As for omeprazole sulfone, it was significantly delayed in poor metabolizers (4.7 ± 0.4 h) compared with homozygous or heterozygous extensive metabolizers (2.8 ± 0.3 h or 3.0 ± 0.6 h, respectively). The values of $t_{1/2}$ of omeprazole and omeprazole sulfone were

Table II. Pharmacokinetic Parameters of Omeprazole and Its Two Metabolites in Three Groups Classified by *CYP2C19* Genotype

	Study group[a]					
	Homozygous extensive metabolizers (HomoEMs) (n = 6)	Heterozygous extensive metabolizers (HeteroEMs) (n = 6)	Poor metabolizers (PMs) (n = 6)	HomoEMs versus HeteroEMs[b]	HomoEMs versus PMs[b]	HeteroEMs versus PMs[b]
Omeprazole[c]						
AUC (ng · h/ml)	618.3 ± 141.9	1061.8 ± 269.2	4587.1 ± 681.6	NS	$p < 0.01$	$p < 0.01$
C_{max} (ng/ml)	251.1 ± 46.2	623.1 ± 149.1	1070.2 ± 185.3	NT	NT	NT
$t_{1/2}$ (h)	1.09 ± 0.08	1.18 ± 0.20	2.41 ± 0.15	NS	$p < 0.01$	$p < 0.01$
5-Hydroxyomeprazole[c,d]						
AUC (ng · h/ml)	295.6 ± 39.1	409.7 ± 92.6	346.0 ± 148.5	NT	NT	NT
C_{max} (ng/ml)	95.5 ± 14.0	134.0 ± 32.4	40.1 ± 8.4	NS	NS	$p < 0.05$
$t_{1/2}$ (h)	1.41 ± 0.20	1.42 ± 0.36	1.81 ± 0.41	NT	NT	NT
$AUC_{H\text{-}OPZ}/AUC_{OPZ}$	0.565 ± 0.100	0.479 ± 0.091	0.079 ± 0.030	NS	$p < 0.01$	$p < 0.05$
Omeprazole sulfone[c,e]						
AUC (ng · h/ml)	357.8 ± 75.7	720.7 ± 143.2	2794.7 ± 414.4	NS	$p < 0.01$	$p < 0.01$
C_{max} (ng/ml)	72.1 ± 11.0	110.9 ± 11.4	258.9 ± 32.4	NS	$p < 0.01$	$p < 0.01$
$t_{1/2}$ (h)	2.38 ± 0.3	2.55 ± 0.42	4.52 ± 0.65	NS	$p < 0.05$	$p < 0.05$
$AUC_{OPZ\text{-}SFN}/AUC_{OPZ}$	0.616 ± 0.086	0.628 ± 0.110	0.841 ± 0.086	NT	NT	NT

[a] Each value represents the mean ± SE.
[b] NS; not significant; NT, not tested because of p value more than 0.05 by one-way analysis of variance.
[c] AUC, area under the plasma concentration-time curve up to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life.
[d] $AUC_{H\text{-}OPZ}/AUC_{OPZ}$, a ratio of AUC for 5-hydroxyomeprazole to AUC for omeprazole.
[e] $AUC_{OPZ\text{-}SFN}/AUC_{OPZ}$, a ratio of AUC for omeprazole sulfone to AUC for omeprazole.

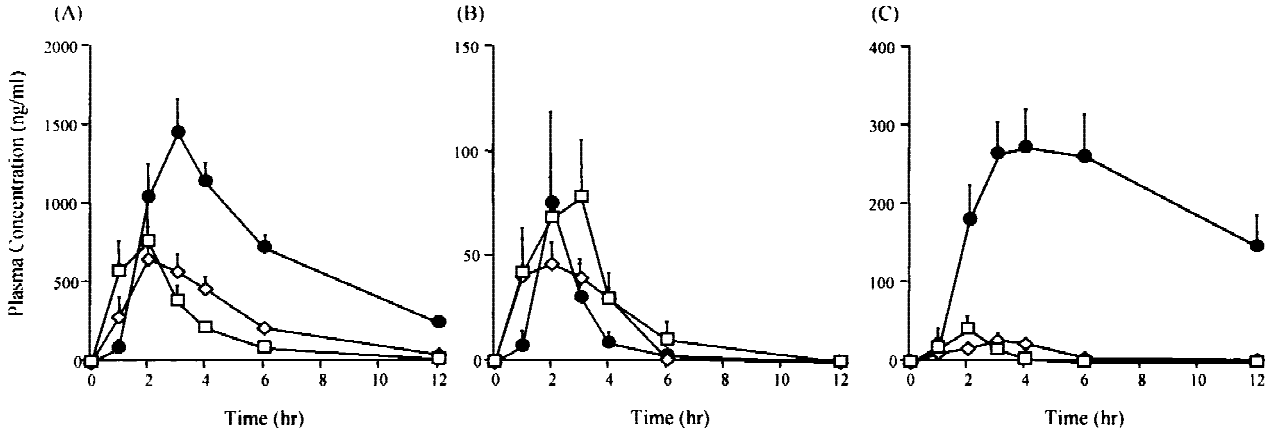

Fig. 2. Plasma concentrations of lansoprazole (A), 5-hydroxylansoprazole (B), and lansoprazole sulfone (C) after a single oral dosing of 30 mg lansoprazole in the homozygous extensive metabolizers (□), heterozygous extensive metabolizers (◇), and poor metabolizers (●) classified by *CYP2C19* genotype. Each point represents the mean ± SE (n = 6).

1.9- and 2.2-fold prolonged in poor metabolizers compared with homozygous extensive metabolizers, but for 5-hydroxyomeprazole, the value was comparable among the three groups. There was no difference in any pharmacokinetic findings of omeprazole, 5-hydroxyomeprazole, and omeprazole sulfone between the homozygous and heterozygous extensive metabolizers.

Lansoprazole

Plasma concentration-time curves of lansoprazole, 5-hydroxylansoprazole, and lansoprazole sulfone after 30 mg lansoprazole administration in the homozygous extensive metabolizers, the heterozygous extensive metabolizers, and the poor metabolizers are shown in Fig. 2. Plasma concentrations of lansoprazole and lansoprazole sulfone in poor metabolizers were much higher than those in homozygous or heterozygous extensive metabolizers, being similar to omeprazole; whereas the 5-hydroxylansoprazole concentrations in poor metabolizers were slightly lower. Table III lists the pharmacokinetic parameters. The value of the AUC of lansoprazole in poor metabolizers was 3.7- and 2.7-fold higher than that in homozygous and heterozygous extensive metabolizers, respectively. The AUC of lansoprazole sulfone was also higher in poor metabolizers, whereas the AUC of 5-hydroxylansoprazole was comparable among the three groups. After the correction of the AUC of 5-hydroxylansoprazole or lansoprazole sulfone by that of the parent lansoprazole, it was significantly lower in poor metabolizers for 5-hydroxylansoprazole, but was still predominant in poor metabolizers for lansoprazole sulfone. The values of C_{max} also suggested differences among the three groups similar to the AUC, but showed weaker

Table III. Pharmacokinetic Parameters of Lansoprazole and Its Two Metabolites in Three Groups Classified by *CYP2C19* Genotype

	Study group[a]					
	Homozygous extensive metabolizers (HomoEMs) (n = 6)	Heterozygous extensive metabolizers (HeteroEMs) (n = 6)	Poor metabolizers (PMs) (n = 6)	HomoEMs versus HeteroEMs[b]	HomoEMs versus PMs[b]	HeteroEMs versus PMs[b]
Lansoprazole[c]						
AUC (ng · h/ml)	2549.3 ± 371.9	3484.2 ± 567.3	9379.7 ± 978.2	NS	$p < 0.01$	$p < 0.01$
C_{max} (ng/ml)	849.3 ± 146.7	955.4 ± 197.3	1550.1 ± 218.8	NS	NS	NS
$t_{1/2}$ (h)	2.01 ± 0.62	2.47 ± 0.29	3.77 ± 0.31	NS	$p < 0.05$	NS
5-Hydroxylansoprazole[c,d]						
AUC (ng · h/ml)	276.5 ± 69.4	182.5 ± 19.9	140.7 ± 56.6	NT	NT	NT
C_{max} (ng/ml)	118.6 ± 19.2	71.5 ± 14.0	82.2 ± 41.3	NT	NT	NT
$t_{1/2}$ (h)	1.10 ± 0.41	0.71 ± 0.11	0.63 ± 0.13	NT	NT	NT
$AUC_{H\text{-}LPZ}/AUC_{LPZ}$	0.127 ± 0.047	0.060 ± 0.013	0.013 ± 0.005	NS	$p < 0.05$	NS
Lansoprazole sulfone[c,e]						
AUC (ng · h/ml)	81.5 ± 21.4	177.5 ± 70.3	3844.6 ± 693.3	NS	$p < 0.01$	$p < 0.01$
C_{max} (ng/ml)	49.3 ± 13.5	46.1 ± 8.0	309.1 ± 42.5	NS	$p < 0.01$	$p < 0.01$
$t_{1/2}$ (h)	0.48 ± 0.10	0.62 ± 0.30	5.28 ± 0.99	NS	$p < 0.01$	$p < 0.01$
$AUC_{LPZ\text{-}SFN}/AUC_{LPZ}$	0.037 ± 0.014	0.044 ± 0.011	0.399 ± 0.077	NS	$p < 0.01$	$p < 0.01$

[a] Each value represents the mean ± SE.
[b] NS; not significant; NT, not tested because of p value more than 0.05 by one-way analysis of variance.
[c] AUC, area under the plasma concentration-time curve up to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life.
[d] $AUC_{H\text{-}LPZ}/AUC_{LPZ}$, a ratio of AUC for 5-hydroxylansoprazole to AUC for lansoprazole.
[e] $AUC_{LPZ\text{-}SFN}/AUC_{LPZ}$, a ratio of AUC for lansoprazole sulfone to AUC for lansoprazole.

power to find statistical significance. The maximum concentration of lansoprazole and 5-hydroxylansoprazole was achieved at 1.8–2.8 h after administration for all groups. Lansoprazole sulfone was delayed in poor metabolizers (4.3 ± 0.6 hr) compared with homozygous or heterozygous extensive metabolizers (1.8 ± 0.2 h and 2.2 ± 0.3 h, respectively). The values of $t_{1/2}$ of lansoprazole and lansoprazole sulfone were 1.9- and 11.0-fold prolonged in poor metabolizers compared with homozygous extensive metabolizers, but there was no statistical significance in the 5-hydroxylansoprazole elimination rate among the three groups. There was no statistical significance in any pharmacokinetic findings of lansoprazole, 5-hydroxylansoprazole, and lansoprazole sulfone between the homozygous and heterozygous extensive metabolizers.

Rabeprazole

Figure 3 shows the plasma concentration-time curves of rabeprazole, thioether rabeprazole, and rabeprazole sulfone after 20 mg sodium rabeprazole administration in the homozygous extensive metabolizers, the heterozygous extensive metabolizers, and the poor metabolizers, which were classified by the *CYP2C19* genotype. The plasma concentrations of rabeprazole, thioether rabeprazole, and rabeprazole sulfone were similar among the three groups. The pharmacokinetic parameters listed in Table IV also suggested no relationship between the *CYP2C19* genotype and the pharmacokinetics of rabeprazole.

DISCUSSION

Recent developments in pharmacogenomics have suggested that the genetic polymorphism of drug metabolizing enzymes and/or target enzymes and receptors are responsible for interindividual variations in efficacy and adverse events. Genetic information was obtained for a number of drug metabolizing enzymes, and consequently their genotyping has been of interest as an alternative to therapeutic drug monitoring, which is presently used worldwide to optimize the dosage regimen for each patient, since administration of the drug is not necessary. The correlation between the genotype and phenotype should be clarified for the application of clinical genotyping, that is, the pharmacokinetics and pharmacodynamics, and the predictability of the phenotype based on the genotype.

CYP2C19 genotype-related pharmacokinetics of omeprazole has been demonstrated in some clinical reports (20,21). This is the first report for the effect of the *CYP2C19* genotype on the pharmacokinetics of lansoprazole, in which omeprazole, lansoprazole, and rabeprazole were compared using the same subjects in a crossover manner. In the present study, it was clarified that the plasma concentrations of omeprazole and lansoprazole were well correlated with the *CYP2C19* genotype, suggesting the *CYP2C19* genotype dependence in anti-*H. pylori* therapy, even when lansoprazole was used as the PPI. However, the ratio of the AUC for lansoprazole in poor metabolizers compared with extensive metabolizers was lower when compared with omeprazole, and this suggested the lower dependence on the *CYP2C19* genotype in the therapy, but encouraged further clinical investigations. In contrast, there was no *CYP2C19* genetic effect on the pharmacokinetics of rabeprazole, suggesting the lack of *CYP2C19* genotype dependence. *In vitro* human microsome studies have suggested that rabeprazole was also metabolized to demethyl rabeprazole by CYP2C19 (10). This could be explained by *in vitro–in vivo* differences or the relatively larger contribution of nonenzymatic metabolism to thioether rabeprazole and CYP3A4 to rabeprazole sulfone (15,28).

It was also demonstrated that the *CYP2C19* genotype dependence of plasma concentrations of omeprazole and lansoprazole could be explained by 5-hydroxylation rather than sulfone formation. The plasma concentrations of 5-hydroxyomeprazole and 5-hydroxylansoprazole were apparently similar among the three groups, and those of omeprazole sulfone and lansoprazole sulfone were significantly higher in poor metabolizers than in extensive metabolizers. However, these depended on the concentrations of their parent omeprazole and lansoprazole, respectively. Thus, to clarify the metabolic process, the AUC values of these metabolites were corrected by dividing them by the AUC value of each parent PPI. It was demonstrated that 5-hydroxylation of omeprazole was decreased in poor metabolizers compared with extensive me-

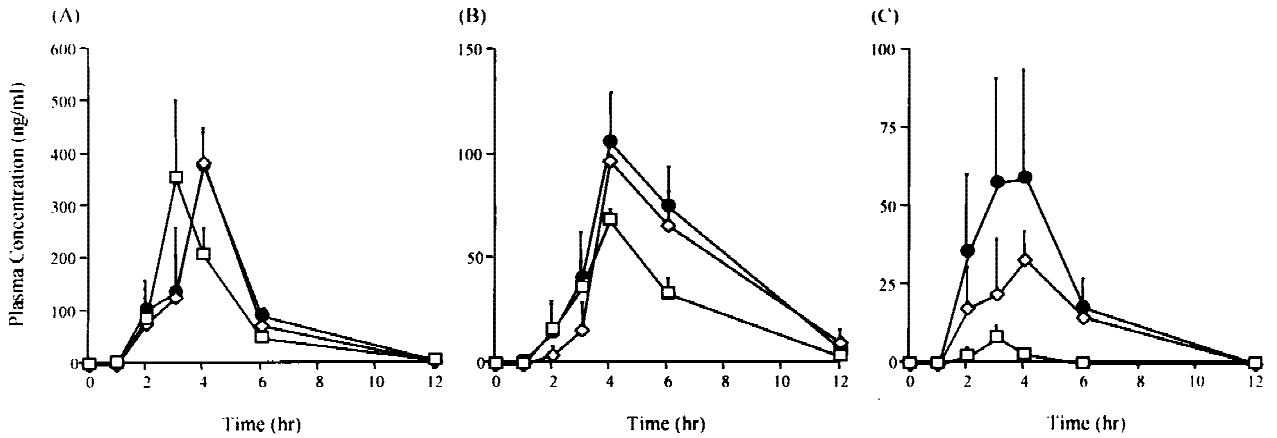

Fig. 3. Plasma concentrations of rabeprazole (A), thioether rabeprazole (B), and rabeprazole sulfone (C) after a single oral dosing of 20 mg sodium rabeprazole in homozygous extensive metabolizers (□), heterozygous extensive metabolizers (◇), and poor metabolizers (●) classified by *CYP2C19* genotype. Each point represents the mean ± SE (n = 6).

Table IV. Pharmacokinetic Parameters of Rabeprazole and Its Two Metabolites in Three Groups Classified by *CYP2C19* Genotype

	Study group[a]					
	Homozygous extensive metabolizers (HomoEMs) (n = 6)	Heterozygous extensive metabolizers (HeteroEMs) (n = 6)	Poor metabolizers (PMs) (n = 6)	HomoEMs versus HeteroEMs[b]	HomoEMs versus PMs[b]	HeteroEMs versus PMs[b]
Rabeprazole[c]						
AUC (ng · h/ml)	1048.0 ± 210.2	1114.0 ± 74.6	1240.5 ± 182.6	NT	NT	NT
C_{max} (ng/ml)	449.0 ± 121.8	492.6 ± 67.9	388.3 ± 56.9	NT	NT	NT
$t_{1/2}$ (h)	1.13 ± 0.14	1.39 ± 0.20	1.54 ± 0.29	NT	NT	NT
Thioether-rabeprazole[c, d]						
AUC (ng · h/ml)	316.0 ± 48.7	528.3 ± 121.7	564.2 ± 81.9	NT	NT	NT
C_{max} (ng/ml)	74.1 ± 3.9	108.5 ± 8.8	132.2 ± 15.7	NS	$p < 0.01$	NS
$t_{1/2}$ (h)	1.64 ± 0.28	1.66 ± 0.16	1.76 ± 0.27	NT	NT	NT
$AUC_{T\text{-}RPZ}/AUC_{RPZ}$	0.389 ± 0.115	0.481 ± 0.118	0.517 ± 0.129	NT	NT	NT
Rabeprazole sulfone[c, e]						
AUC (ng · h/ml)	15.9 ± 3.0	151.1 ± 89.1	256.2 ± 133.2	NT	NT	NT
C_{max} (ng/ml)	11.6 ± 2.3	44.7 ± 14.1	79.6 ± 33.7	NT	NT	NT
$t_{1/2}$ (h)	0.53 ± 0.05	0.82 ± 0.10	0.83 ± 0.12	NT	NT	NT
$AUC_{RPZ\text{-}SFN}/AUC_{RPZ}$	0.017 ± 0.003	0.153 ± 0.097	0.184 ± 0.070	NT	NT	NT

[a] Each value represents the mean ± SE.
[b] NS; not significant; NT, not tested because of p value more than 0.05 by one-way analysis of variance.
[c] AUC, area under the plasma concentration-time curve up to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life.
[d] $AUC_{T\text{-}RPZ}/AUC_{RPZ}$, a ratio of AUC for thioether rabeprazole to AUC for rabeprazole.
[e] $AUC_{RPZ\text{-}SFN}/AUC_{RPZ}$, a ratio of AUC for rabeprazole sulfone to AUC for rabeprazole.

tabolizers, with no alteration of its sulfone formation. This was not contradictory to the *in vitro* findings on the omeprazole metabolism using human liver microsomes (7,8), which demonstrated that CYP2C19 was the responsible enzyme for 5-hydroxylation of omeprazole. As for lansoprazole, 5-hydroxylation was shown to be decreased, but interestingly, sulfone formation was increased in poor metabolizers.

There has been no rational conclusion concerning the stratification of subjects based on genotype. Theoretically, phenotype should be the square of the genotype, but posterior factors sometimes affect the contribution of inherent factors. For example, a total of 17 mutant alleles have been identified in the *N-acetyltransferase2* (*NAT2)* gene, which is responsible for NAT2 activity, but it has been accepted that its phenotype could be classified into only three groups (29). As for *CYP2C19* gene, two mutant alleles—*CYP2C19*2* and *CYP2C19*3*—have been found with wild-type allele *CYP2C19*1,* and the metabolic activity of the former two was almost negligible. Therefore, the subjects could be stratified rationally into three groups (30,31). However, it was suggested that the discrimination of heterozygous *CYP2C19*1* from homozygous *CYP2C19*1* was not always necessary.

In the anti-*H. pylori* therapy, it has been empirically recommended that the dose of PPI or antimicrobials be increased to ensure a higher eradication rate (32); therefore, the effective and safe dosage regimen could not still be determined. We found that the efficacy of anti-*H. pylori* using omeprazole and antimicrobials was related to the *CYP2C19* genotype (22,23). A possible explanation is that the antiacid secretion of omeprazole was expected to be more potent in poor metabolizers than in extensive metabolizers because of the more extensive exposure to omeprazole. Then, the higher intragastric pH and increased susceptibility and stability of antimicrobials (33,34) might determine the success of the anti-*H. pylori* therapy.

In conclusion, *CYP2C19* genotype dependence will be found in anti-*H. pylori* therapy when lansoprazole is used as the PPI, and the discrimination of heterozygous and homozygous *CYP2C19*1* will not always be necessary when the patients are stratified based on the *CYP2C19* genotype.

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REFERENCES

1. A. S. Guerreiro, B. C. Neves, and M. G. Quina. Omeprazole in the treatment of peptic ulcers resistant to H_2-receptor antagonists. *Aliment. Pharmacol. Ther.* **4**:309–313 (1990).
2. W. L. Peterson. *Helicobacter pylori* and peptic ulcer disease. *N. Engl. J. Med.* **324**:1043–1048 (1991).
3. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. *J. Am. Med. Assoc.* **272**:65–69 (1994).
4. J. Parsonnet, G. D. Friedman, D. P. Vandersteen, Y. Chang, J. H. Vogelman, N. Orentreich, and R. K. Sibley. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N. Engl. J. Med.* **325**: 1127–1131 (1991).
5. L. E. Hansson, L. Engstrand, O. Nyrén, D. J. Evans, A. Lindgren, R. Bergström, B. Andersson, L. Athlin, O. Bendtsen, and P. Tracz. *Helicobacter pylori* infection: Independent risk indicator of gastric adenocarcinoma. *Gastroenterology* **105**:1098–1103 (1993).
6. T. Lind, F. Megraud, P. Unge, E. Bayerdorffer, C. O'Morain, and R. Spiller, and others. The MACH2 study: Role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. *Gastroenterology* **116:**248–253 (1999).
7. K. Chiba, K. Kobayashi, K. Manabe, M. Tani, T. Kamataki, and T. Ishizaki. Oxidative metabolism of omeprazole in human liver microsomes: Cosegregation with *S*-mephenytoin 4′-hydroxylation. *J. Pharmacol. Exp. Ther.* **266**:52–59 (1993).
8. T. Andersson, J. O. Miners, M. E. Veronese, and D. J. Birkett. Identification of human liver cytochrome P450 isoforms mediating secondary omeprazole metabolism. *Br. J. Clin. Pharmacol.* **37**:597–604 (1994).

9. L. Pichard, R. Curi-Pedrosa, C. Bonfils, E. Jacqz-Aigrain, J. Domergue, and H. Joyeux. Oxidative metabolism of lansoprazole by human liver cytochromes P450. *Mol. Pharmacol.* **47**:410–418 (1995).
10. M. Vanderbranden, B. J. Ring, S. N. Binkley, and S. A. Wrighton. Interaction of human liver cytochromes P450 in vitro with LY307640, a gastric proton pump inhibitor. *Pharmacogenetics* **6**:81–91 (1996).
11. D. R. Sohn, K. Kobayashi, K. Chiba, K. H. Lee, S. G. Shin, and T. Ishizaki. Disposition kinetics and metabolism of omeprazole in extensive and poor metabolizers of *S*-mephenytoin 4′-hydroxylation recruited from an Oriental population. *J. Pharmacol. Exp. Ther.* **262**:1195–1202 (1992).
12. J. D. Balian, N. Sukhova, J. W. Harris, J. Hewett, L. Pickle, J. A. Goldstein, R. L. Woosley, and D. A. Flockhart. The hydroxylation of omeprazole correlates with *S*-mephenytoin metabolism: A population study. *Clin. Pharmacol. Ther.* **57**:662–669 (1995).
13. T. Ishizaki, D. R. Sohn, K. Kobayashi, K. Chiba, K. H. Lee, and S. G. Shin. Interethnic differences in omeprazole metabolism in the two *S*-mephenytoin hydroxylation phenotypes studied in Caucasians and Orientals. *Ther. Drug. Monit.* **16**:214–215 (1994).
14. D. R. Sohn, J. T. Kwon, H. K. Kim, and T. Ishizaki. Metabolic disposition of lansoprazole in relation to the *S*-mephenytoin 4′-hydroxylation phenotype status. *Clin. Pharmacol. Ther.* **61**:574–582 (1997).
15. S. Yasuda, Y. Horai, Y. Tomono, H. Nakai, C. Yamato, K. Manabe, K. Kobayashi, K. Chiba, and T. Ishizaki. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4—Hydroxylation status. *Clin. Pharmacol. Ther.* **58**:143–154 (1995).
16. T. Ishizaki and Y. Horai. Review article: Cytochrome P450 and the metabolism of proton pump inhibitors—Emphasis on rabeprazole. *Aliment. Pharmacol. Ther.* **13**:27–36 (1999).
17. S. M. F. de Morais, G. R. Wilkinson, J. Blaisdell, K. Nakamura, U. A. Meyer, and J. A. Goldstein. The major genetic defect responsible for the polymorphism of *S*-mephenytoin metabolism in humans. *J. Biol. Chem.* **269**:15419–15422 (1994).
18. S. M. F. de Morais, G. R. Wilkinson, J. Blaisdell, U. A. Meyer, K. Nakamura, and J. A. Goldstein. Identification of a new genetic defect responsible for the polymorphism of (*S*)-mephenytoin metabolism in Japanese. *Mol. Pharmacol.* **46**:594–598 (1994).
19. J. A. Goldstein and S. M. F. de Morais. Biochemistry and molecular biology of the human CYP2C subfamily. *Parmacogenetics* **4**:285–299 (1994).
20. I. Ieiri, T. Kubota, A. Urae, M. Kimura, Y. Wada, K. Mamiya, S. Yoshioka, S. Irie, T. Amamoto, K. Nakamura, and others. Pharmacokinetics of omeprazole (a substrate of CYP2C19) and comparison with two mutant alleles, $CYP2C19_{m1}$ in exon 5 and $CYP2C19_{m2}$ in exon 4, in Japanese subjects. *Clin. Pharmacol. Ther.* **59**:647–653 (1996).
21. T. Furuta, K. Ohashi, K. Kosuge, X. J. Zhao, M. Takashima, M. Kimura, M. Nishimoto, H. Hanai, E. Kaneko, and T. Ishizaki. *CYP2C19* genotype status and effect of omeprazole on intragastric pH in humans. *Clin. Pharmacol. Ther.* **65**:552–561 (1999).
22. Y. Tanigawara, N. Aoyama, T. Kita, K. Shirakawa, F. Komada, M. Kasuga, and K. Okumura. *CYP2C19* genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. *Clin. Pharmacol. Ther.* **66**:528–534 (1999).
23. N. Aoyama, Y. Tanigawara, T. Kita, T. Sakai, K. Shirakawa, D. Shirasaka, F. Komada, K. Okumura, and M. Kasuga. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for *Helicobacter pylori* eradication in cytochrome P450 2C19 poor metabolizers. *J. Gastroenterol.* **34**:80–83 (1999).
24. K. Kobayashi, K. Chiba, D. R. Shon, Y. Kato, and T. Ishizaki. Simultaneous determination of omeprazole and its metabolites in plasma and urine by reversed-phase high-performance liquid chromatography with an alkaline-resistant polymer-coated C_{18} column. *J. Chromatogr.* **579**:299–305 (1992).
25. I. Aoki, M. Okumura, and T. Yashiki. High-performance liquid chromatographic determination of lansoprazole and metabolites in human serum and urine. *J. Chromatogr.* **571**:283–290 (1991).
26. M. D. Karol, G. R. Granneman, and K. Alexander. Determination of lansoprazole and five metabolites in plasma by high-performance liquid chromatography. *J. Chromatogr. B* **668**:182–186 (1995).
27. H. Nakai, Y. Shimamura, T. Kanazawa, S. Yasuda, and M. Kayano. Determination of a new H^+-K^+ ATPase inhibitor (E3810) and its four metabolites in human plasma by high-performance liquid chromatography. *J. Chromatogr. B* **660**:211–220 (1994).
28. T. J. Humphries and G. J. Merritt. Review article: Drug interactions with agents used to treat acid-related diseases. *Aliment. Pharmacol. Ther.* **13**:18–26 (1999).
29. K. P. Vatsis, W. W. Weber, D. A. Bell, J. M. Dupret, D. A. Evans, D. M. Grant, D. W. Hein, H. J. Lin, U. A. Meyer, and M. V. Relling. Nomenclature for N-acetyltransferases. *Pharmacogenetics* **5**:1–17 (1995).
30. M. Chang, G. Tybring, M. -L. Dahl, E. Gótharson, M. Sagar, R. Seensalu, and L. Bertilsson. Interphenotype differences in disposition and effect on gastric levels of omeprazole—Suitability of omeprazole as a probe for CYP2C19. *Br. J. Clin. Pharmacol.* **39**:511–518 (1995).
31. T. Furuta, K. Ohashi, T. Kamata, M. Takashima, K. Kosuge, T. Kawasaki, H. Hanai, T. Kubota, T. Ishizaki, and E. Kaneko. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann. Intern. Med.* **129**:1027–1030 (1998).
32. D. Y. Graham, G. M. Lew, P. D. Klein, D. G. Evans, D. J. Evans Jr., Z. A. Saeed, and H. M. Malaty. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Ann. Intern. Med.* **116**:705–708 (1992).
33. A. F. Goddard, M. J. Jessa, D. A. Barrett, P. N. Shaw, J. P. Idström, C. Cederberg, and R. C. Spiller. Effect of omeprazole on the distribution of metronidazole, amoxicillin, and clarithromycin in human gastric juice. *Gastroenterology* **111**:358–367 (1996).
34. G. Cederbrant, G. Kahlmeter, C. Schalen, and C. Kamme. Additive effect of clarithromycin combined with 14-hydroxy clarithromycin, erythromicin, amoxicillin, metronidazole or omeprazole against *Helicobacter pylori*. *J. Antimicrob. Chemother.* **34**: 1025–1029 (1994).