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Effects of *CYP2C19* Genetic Polymorphisms on PK/PD Responses of Omeprazole in Korean Healthy Volunteers

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The aim of this study was to examine the effects of *CYP2C19*2* and **3* genetic polymorphisms on omeprazole pharmacokinetic (PK) and pharmacodynamic (PD) responses. Twenty-four healthy Korean volunteers were enrolled and given 20 mg omeprazole orally once daily for 8 days. The genotypes of *CYP2C19* single nucleotide polymorphisms (SNPs) (**2*, **3*, and **17*) were screened. The plasma concentrations of omeprazole, omeprazole sulfone, and 5-hydroxy (5-OH) omeprazole were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS). The noncompartmental method was used for the determination of PK parameters. Change of mean pH and proportion (%) of time of gastric pH above 4.0 were estimated. The poor metabolizer (PM) group had the lowest metabolic ratio and exhibited the highest area under the curve (AUC) for omeprazole among the *CYP2C19* phenotype groups. The PM group showed the greatest change of mean pH and the highest % time of gastric pH above 4.0. The relationship between AUC of omeprazole and % time of gastric pH above 4.0 was confirmed. The study demonstrates that *CYP2C19*2* and **3* influence the PKs and PDs of omeprazole in Korean healthy volunteers. Clinical trial registry at the U.S. National Institutes of Health (https://clinicaltrials.gov), number NCT02299687.

Keywords: Omeprazole; *CYP2C19*; Genetic Polymorphisms

INTRODUCTION

Proton pump inhibitors (PPIs) are widely used for the treatment of gastro-esophageal reflux disease (GERD) and various acid-related disorders. It has been reported that sales of PPIs are in excess of $10 billion per year (1), and adverse drug events have increased from 30,000 to 90,000 events from 1998 to 2005 (2). All PPIs have a common pyridinyl sulphinyl benzimidazole backbone and are extensively metabolized into inactive metabolites by cytochrome P450 (CYP) enzymes in the liver (3).

Omeprazole, the prototype of the PPIs, undergoes biotransformation into 2 major metabolites, 5-hydroxy (5-OH) omeprazole and omeprazole sulfone, after oral administration through the action of *CYP2C19* and *CYP3A4* in the liver (4-8). These metabolites are inactive and transformed into 5-OH omeprazole sulfone by *CYP3A4* and *CYP2C19* thereafter. The affinity of omeprazole for *CYP2C19* has been reported to be approximately 10 times greater than for *CYP3A4* (9). A minor metabolite, 5-O-demethylomeprazole, has been identified, but does not have an effect on gastric acid secretion (10). The metabolism of omeprazole is shown in Fig. 1.

Omeprazole has a chiral center and is administered as a racemic mixture of the *S*- and *R*-enantiomers. *R*- and *S*-omeprazole show stereoselective disposition because of the enzyme-catalyzed stereoselective metabolism that results in lower metabolic stability of its *R*-isomer and the racemate compared with the *S*-isomer (esomeprazole) (11,12). Racemic omeprazole is more susceptible to the metabolic enzyme than esomeprazole. Of the 4 main PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole), omeprazole is most affected by *CYP2C19* genetic polymorphisms (13,14). Due to differences in hepatic enzyme activity, the pharmacokinetics (PKs) of omeprazole shows extensive inter-individual variability that may lead to poor predictability of treatment-related outcomes and adverse effects (15). Considering that the main metabolite is 5-OH omeprazole, *CYP2C19* has an important role in omeprazole metabolism and

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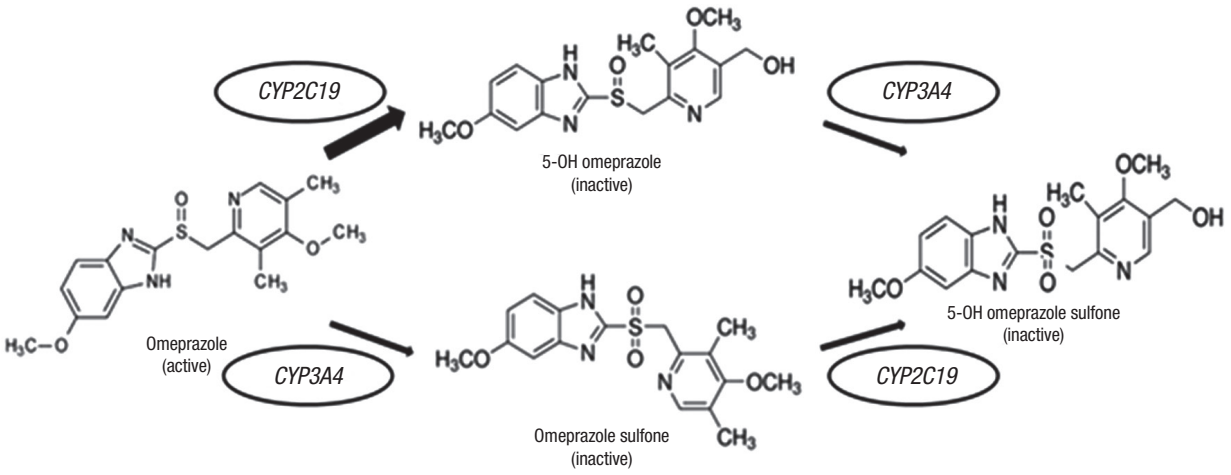

Fig. 1. Metabolism of omeprazole.

therapeutic response.

Numerous studies have shown that *CYP2C19* genetic polymorphisms affect enzyme activity and cause large individual PK variations (2). Many studies regarding *CYP2C19* genetic polymorphisms have focused on *CYP2C19*2* and **3*, finding that **2* (G681A) and **3* (G636A) variations reduce enzyme activity (16-21). *CYP2C19*17* carrying –806C>T and –3402C>T in the 5'-flanking region was found to be associated with increased *CYP2C19* gene transcription in 2006 (22). The Dutch Pharmacogenomics Working Group recommends omeprazole dose alteration according to *CYP2C19*17* allele (23). However, dose alterations based on *CYP2C19*2* and **3* genetic polymorphisms for omeprazole treatment are not provided. Notably, phenotyping of *CYP2C19* revealed that the prevalence of poor metabolizers (PMs) in the Asian population was 13%–23%, while the prevalence of PMs among Europeans and Africans was 3%–6% (24). It has been reported that 2 single base pair mutations (*CYP2C19*2* and **3*) define greater than 99% of the PM allele in Asian populations (24). Therefore, it is important to assess the effects of *CYP2C19*2* and **3* genetic polymorphisms during omeprazole therapy in a Korean population.

On the other hand, several studies have reported increased the area under the curve (AUC) of omeprazole after multiple dosing of omeprazole (25,26). It is possible that first-pass elimination of omeprazole decreased after repeated administration, or the stability of the formulation could increase owing to degradation of omeprazole in acidic media. One study has shown that omeprazole inhibits the activity of *CYP2C19* after repeated administration, probably owing to its sulfone metabolites (27). The effect of *CYP2C19* genetic polymorphisms on omeprazole PK/pharmacodynamics (PDs) needs to be studied in the context of repeated administration and cannot be assessed on the basis of studies that use single doses only.

The aim of this study was therefore to assess the effects of *CYP2C19*2* and **3* genetic polymorphisms on omeprazole PK and PD response following single and multiple dosing. Along with other studies, this study should provide evidence for dosing alteration and help to make omeprazole dose recommendations in relation to *CYP2C19*2* and **3* genotypes.

MATERIALS AND METHODS

Subjects

Healthy Korean volunteers were enrolled in the present study after giving written informed consent at Seoul National University Hospital during September to November 2014. Participants (20–45 years old) were recruited after *CYP2C19* genotyping until 8 subjects were included in each *CYP2C19* phenotypic group. Men with a body weight of 55 kg to 90 kg and women with a body weight of 50 kg to 90 kg were included. Subjects with body mass index (BMI) of between 18 and 25 were included. Smoking (more than 10 cigarettes/day) and alcohol consumption (more than 21 units/week or 10 g of pure alcohol) was a ground for the exclusion of volunteers. Women with child-bearing potential were also excluded. Volunteers who had the *CYP2C19*17* mutation allele which is likely to cause an increase in omeprazole metabolism, were excluded. During the treatment period, smoking and alcohol, grape juice and caffeine consumption were prohibited.

Study design and data collection

This study was open-label and multiple dose PK/PD study. The trial profile of the present study is shown in Fig. 2. Subjects were given 20 mg omeprazole as enteric coated granules (Losec®; Yuhan Pharm., Seoul, Korea) orally once daily on an empty stomach for 8 days. Plasma samples were collected at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after the first and last dose (day 8) of omeprazole, and stored at –70°C until analysis. To assess the PD effect, intragastric pH (24 hours) was monitored on day 1 (first dosing) and day 8 (last dosing), and a baseline pH profile was

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obtained prior to administration of omeprazole.

CYP2C19 genotyping

Genomic DNA from the blood of study volunteers was extracted by means of the QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany) according to the standard protocol recommended by the manufacturer. Genomic DNA flanking the SNP of interest was amplified by a polymerase chain reaction (PCR) with forward and reverse primer pairs and standard PCR reagents. The genotypes of 3 *CYP2C19* single nucleotide polymorphisms (SNPs) (**2*; rs4244285, **3*; rs4986893, and **17*; rs12248560) were screened by application of a single base extension assay, namely, of the ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA, USA) according to manufacturer's instructions. Table 1 shows the primer sets and probe sequences that were used in the SNaPshot assay.

Analysis of plasma omeprazole concentration

Plasma concentrations of omeprazole, omeprazole sulfone, 5-OH omeprazole, and lansoprazole (internal standard) were determined by ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) with some modifications (28,29). Standard, quality control (QC), and volunteer samples were prepared by extraction with methyl t-butyl ether (MTBE). The mobile phase consisted of 0.1% formic acid in 2 mM ammonium acetate and acetonitrile and gradient elution method was used with a flow rate of 0.3 mL/min. A UPLC system (Waters UPLC; Waters Corp., Parsippany, NJ, USA) with mass spectrometer (Waters Xevo TQ MS; Waters Corp.) was used.Omeprazole, omeprazole sulfone, 5-OH omeprazole, and lansoprazole (IS) were separated on a BEH C18 column (100 mm × 2.1 mm, 1.7 μm, Waters Corp.). Multiple reaction monitoring (MRM) in negative electrospray ionization (ESI) was employed. The m/Z values of the analytes were as follows: omeprazole (344.22 → 194.07), 5-OH omeprazole (360.22 → 194.07), omeprazole sulfone (360.22 → 146.10) and lansoprazole (368.20 → 164.05). The standard curves were linear in the analyzed concentration range (5–2,000 ng/mL) with $r^2 > 0.99$ for the 3 compounds. The lower limit of quantification (LLOQ) was 5 ng/mL for all analytes.

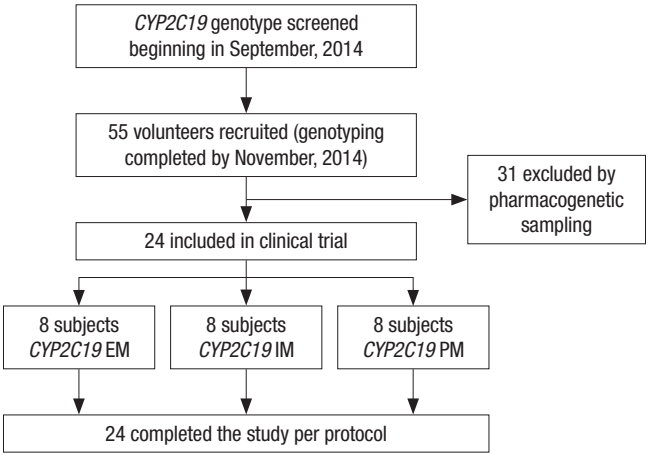

Fig. 2. Trial profile.
PM = poor metabolizer, IM = internal medicine, EM = emergency medicine.

PK/PD and statistical analysis

PK parameters were determined with the noncompartmental method of WinNonlin® (Pharsight Co., Mountain View, CA, USA). The program provided estimates of the area under the concentration time curve from 0 to 12 hours after dosing ($AUC_{0\rightarrow12hr}$) and the area under the concentration time curve from 0 to infinity ($AUC_{infinity}$). Change of mean pH and proportion (%) of time of gastric pH above 4.0 were calculated. Statistical analysis was performed using SAS® version 9.4 software (SAS Institute, Cary, NC, USA) and *P* values < 0.05 were considered to be statistically significant. Differences in baseline characteristics and other parameters of the 3 phenotypic groups (extensive metabolizers, *CYP2C19*1/*1*; intermediate metabolizers, *CYP2C19*1/*2, *1/*3*; PMs, *CYP2C19*2/*2, *2/*3, *3/*3*) were evaluated with the

Table 1. Primer sets and probe sequence for *CYP2C19* genotyping

SNP	Rs number	Variation	Sequence (5'-3')
*CYP2C19*2*	Rs4244285	681G>A	
Forward primer			CAACCAGAGCTTGGCATATTG
Reverse primer			CAAATACGCAAGCAGTCACA
Probe			TCTTAGATATGCAATAATTTTCCCACTATCATTGATTATTTC
*CYP2C19*3*	Rs4986893	636G>A	
Forward primer			CCCTGTGATCCCACTTTCAT
Reverse primer			ATTCACCCCATGGCTGTCTA
Probe			AAAACATCAGGATTGTAAGCACCCCCTG
*CYP2C19*17*	Rs12248560	−806C>T	
Forward primer			GCAGTGATGGAGAAGGGAGA
Reverse primer			TAGCTGGCAGAACTGGGATT
Probe			TTTTTTTTTTCAAATTTGTGTCTTCTGTTCTCAAAG

SNP = single nucleotide polymorphism.

Kruskal-Walis test. The geometric mean ratio (GMR) of metabolic ratios was calculated to compare enzyme activity among *CYP2C19* phenotypic groups (30). Pearson's correlation coefficient was calculated to assess the PK/PD relationship.

Ethics statement

The present study protocol was reviewed and approved by the Ethics Committee of Seoul National University Hospital Institutional Review Board (IRB No. H-1408-072-602). Informed con-

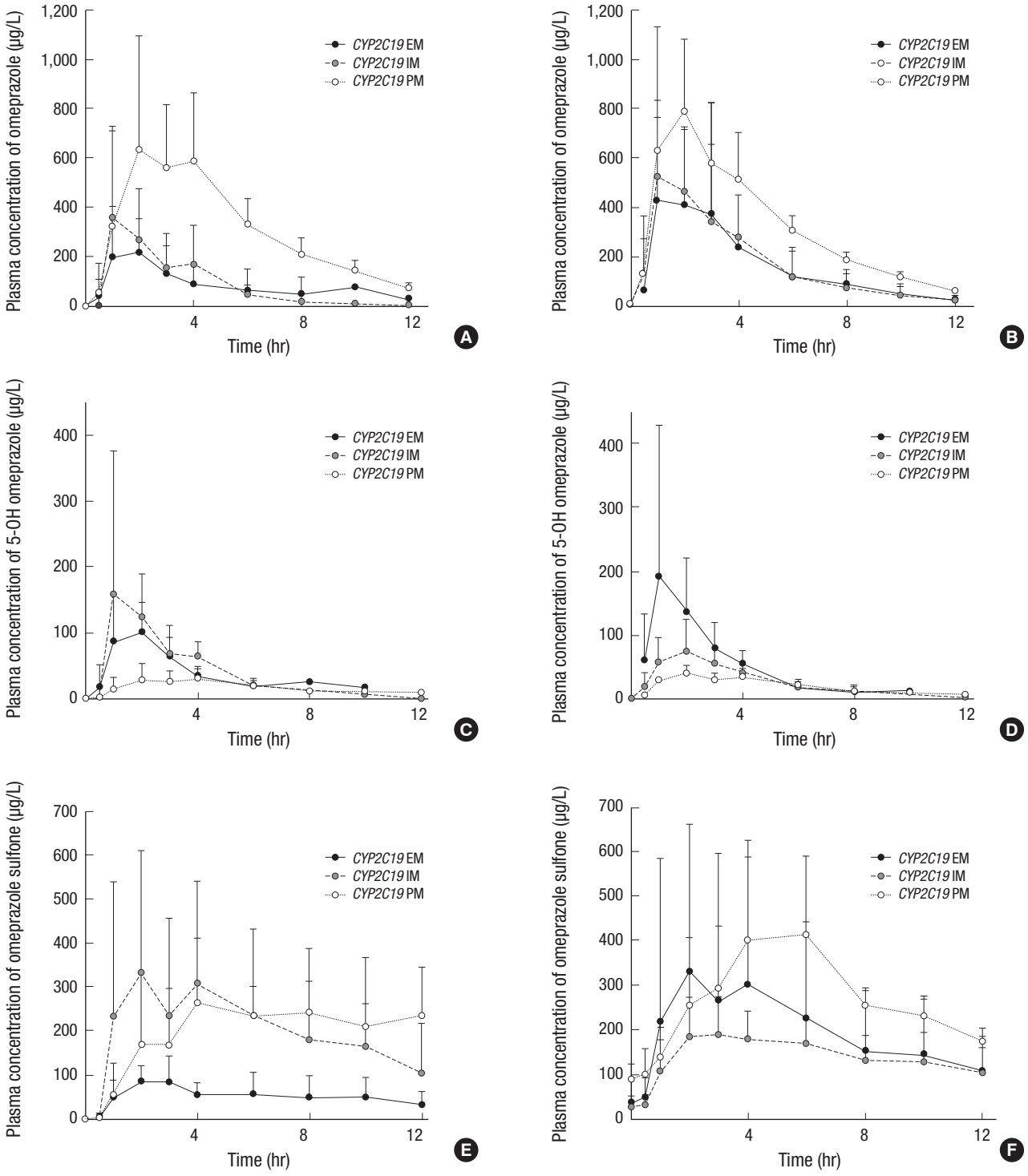

Fig. 3. PK profiles of omeprazole and its metabolites in relation to *CYP2C19* phenotypes. Plasma concentrations of omeprazole, 5-OH omeprazole, and omeprazole sulfone after single dosing (**A**, **C**, **E**), and multiple dosing (**B**, **D**, **F**).
PK = pharmacokinetic, PM = poor metabolizer, IM = internal medicine, EM = emergency medicine.

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sent was submitted by all subjects when they were enrolled. This clinical trial was registered at a service of the U.S. National Institutes of Health (https://clinicaltrials.gov), No. NCT02299687.

RESULTS

Baseline characteristics of volunteers

A total 55 volunteers were recruited, and genotyping was performed for 3 SNPs of *CYP2C19*. To achieve phenotype-stratified sampling, 24 volunteers (8 subjects for each phenotypic group) were included in this clinical study. The mean age was 27.21 ± 4.46 years. The mean body weight and height were 68.59 ± 6.58 kg and 1.74 ± 0.07 m, respectively. The mean BMI was 22.54 ± 1.91 kg/m^2. No statistically significant differences in baseline characteristics (age, mean body weight, height, and BMI) were found among the 3 phenotypic groups.

Effects of *CYP2C19* phenotypes on PKs of omeprazole

Time profiles of mean concentration and standard deviation in the concentration of omeprazole and its metabolites according to *CYP2C19* phenotypes are shown in Fig. 3. Table 2 displays $AUC_{0\rightarrow12hr}$ values of omeprazole, metabolic ratios 5-OH omeprazole ($AUC_{0\rightarrow12hr,\ 5\text{-OH omeprazole/omeprazole}}$) after single and multiple dosing, and the GMRs of the metabolic ratios. The $AUC_{0\rightarrow12hr}$ of omeprazole (active form) in the PM group was higher than in the internal medicine (IM) and emergency medicine (EM) groups after single and multiple dosing. In all 3 groups, the $AUC_{0\rightarrow12hr}$ of omeprazole increased after repeated administration. The metabolic ratio omeprazole sulfone ($AUC_{0\rightarrow12hr,\ 5\text{-OH omeprazole/omeprazole}}$) in the *CYP2C19* PM group was lower than in the EM and IM groups after single dosing (GMR of metabolic ratios = 9.35 and 11.57, respectively). After repeated administration, this trend was maintained but to a lesser degree. With respect to metabolic transformation of omeprazole into omeprazole sulfone, no significant differences in the metabolic ratios were found among the 3 phenotypic groups after multiple dosing.

PK/PD relationship and effects of *CYP2C19* phenotypes on PD response

Fig. 4 shows a significant positive correlation between omepra-

Table 2. The $AUC_{0\rightarrow12hr}$ of omeprazole and metabolic ratios in relation to *CYP2C19* phenotypes after single and multiple dosing

Dosing	PM (n = 8)	IM (n = 6)	EM (n = 8)	GMR (IM/PM)	GMR (EM/PM)
Single dosing					
$AUC_{0\rightarrow12hr,\ omeprazole}$	3,651.57 ± 878.13	972.53 ± 602.87	713.49 ± 555.56	0.24 (0.14–0.42)	0.16 (0.09–0.26)
Metabolic ratio 5-OH omeprazole	0.05 ± 0.01	0.56 ± 0.46	0.68 ± 0.42	9.35 (5.31–16.45)	11.57 (6.85–19.53)
Metabolic ratio omeprazole sulfone	0.65 ± 0.08	2.89 ± 2.63	0.78 ± 0.17	3.00 (1.81–4.98)	1.18 (0.74–1.89)
Multiple dosing					
$AUC_{0\rightarrow12hr,\ omeprazole}$	3,668.83 ± 929.29	2,087.18 ± 1,045.60	1,715.39 ± 1,199.15	0.54 (0.33–0.89)	0.37 (0.22–0.60)
Metabolic ratio 5-OH omeprazole	0.06 ± 0.03	0.16 ± 0.07	0.47 ± 0.39	2.58 (1.41–4.72)	5.59(3.06–10.23)
Metabolic ratio omeprazole sulfone	0.90 ± 0.30	0.87 ± 0.19	2.04 ± 2.39	0.99 (0.59–1.66)	1.46 (0.87–2.46)

The metabolic ratio and $AUC_{0\rightarrow12hr}$ values (μg × hr/L) are given as mean ± standard deviation. GMR values report the geometric mean ratio and 90% confidence interval.
$AUC_{0\rightarrow12hr}$ = area under the concentration time curve from 0 to 12 hour after dosing, $AUC_{0\rightarrow12hr,\ omeprazole}$ = $AUC_{0\rightarrow12hr}$ of omeprazole, $AUC_{0\rightarrow12hr,\ 5\text{-OH omeprazole}}$ = $AUC_{0\rightarrow12hr}$ of 5-hydroxy omeprazole, $AUC_{0\rightarrow12hr,\ omeprazole\ sulfone}$ = $AUC_{0\rightarrow12hr}$ of omeprazole sulfone, PM = poor metabolizer, IM = internal medicine, EM = emergency medicine, GMR = geometric mean ratio, Metabolic ratio 5-OH omeprazole = $AUC_{0\rightarrow12hr,\ 5\text{-OH omeprazole}}/AUC_{0\rightarrow12hr,\ omeprazole}$, Metabolic ratio omeprazole sulfone = $AUC_{0\rightarrow12hr,\ omeprazole\ sulfone}/AUC_{0\rightarrow12hr,\ omeprazole}$.

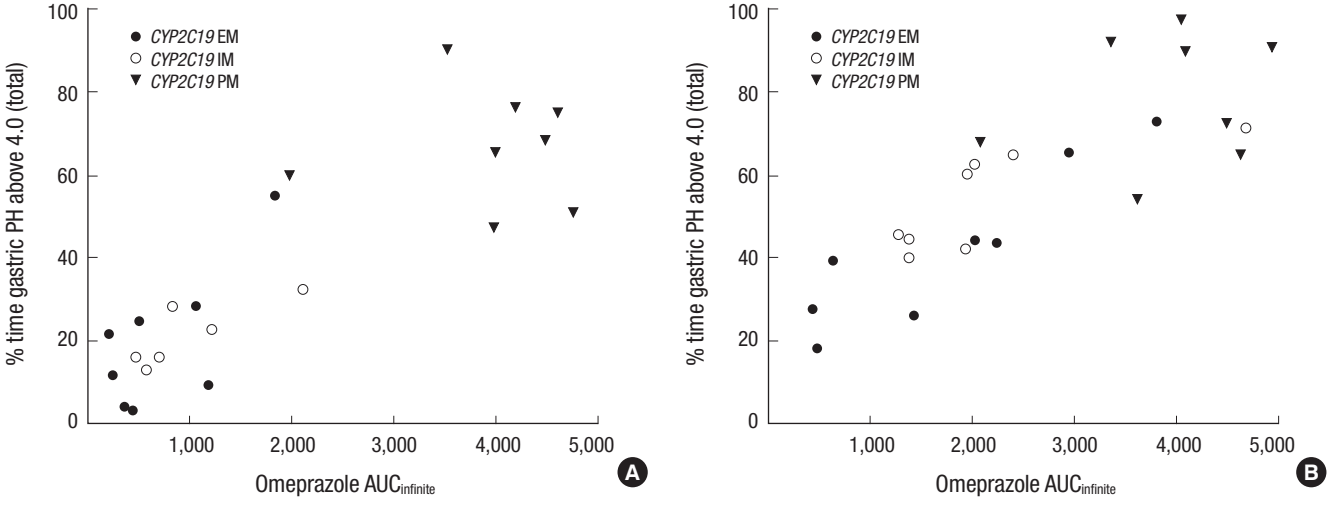

Fig. 4. The correlation of omeprazole $AUC_{infinity}$ and % time gastric pH above 4.0 after single (**A**) and multiple (**B**) dosing.
$AUC_{infinity}$ = area under the concentration time curve from 0 to infinity, PK = pharmacokinetic, PM = poor metabolizer, IM = internal medicine, EM = emergency medicine.

Table 3. Change of mean pH and % time of gastric pH above 4.0 in relation to *CYP2C19* phenotypes

Dosing	PM (n = 8)	IM (n = 8)	EM (n = 8)	*P* value*
Single dosing				
Change of mean pH	2.84 ± 0.48	0.78 ± 0.70	0.71 ± 0.78	0.001
% time gastric pH above 4.0	66.83 ± 14.06	21.43 ± 7.79	19.66 ± 17.07	0.001
Multiple dosing				
Change of mean pH	3.45 ± 0.72	2.19 ± 0.74	1.81 ± 1.02	0.006
% time gastric pH above 4.0	78.99 ± 15.79	53.90 ± 12.10	42.23 ± 19.03	0.005

Variables are given as mean ± standard deviation.
PM = poor metabolizer, IM = internal medicine, EM = emergency medicine.
*Kruskal-Walis test.

zole $AUC_{infinity}$ and % time of gastric pH above 4.0 after single dosing and multiple dosing with Pearson correlation coefficients of 0.861 and 0.826, respectively ($P < 0.001$). Overall, the PD effect was enhanced after repeated administration as $AUC_{0\rightarrow12hr}$ of omeprazole increased.

The change of mean pH and % time of gastric pH above 4.0 after single and multiple dosing are shown in Table 3. The PM group showed a greater change of mean pH than in the IM and EM groups following single ($P = 0.001$) and multiple ($P = 0.006$) omeprazole dosing. Percentage time of gastric pH above 4.0 was greater in the PM group than in the IM and EM groups ($P = 0.001$, $P = 0.005$ for single, multiple dosing, respectively).

DISCUSSION

The aim of this study was to examine the influence of *CYP2C19*2* and **3* genetic polymorphisms on omeprazole PKs and PDs in the context of single and multiple dosing. After administration, omeprazole is primarily transformed into inactive 5-OH omeprazole by *CYP2C19* (9). In this context, *CYP2C19* activity plays an important role in therapeutic response to omeprazole. Well-known genetic polymorphisms of *CYP2C19* that cause inter-individual variability are **2, *3*, and **17*. It has been reported that **2* (G681A point mutation in exon 5) causes a splicing defect and early termination of protein synthesis (2). **3* (G636A single base transition) has been reported to generate a premature stop codon and results in a truncated protein (2). *CYP2C19*17* (–806C>T, –3402C>T) in contrast, is known to increase gene transcription (2). As subjects with **17* mutation allele were excluded, this study was designed to elucidate the effects of *CYP2C19*2* and **3* during omeprazole treatment.

The *CYP2C19* PM (**2/*2, *2/*3* or **3/*3*) group showed the lowest metabolic ratio 5-OH omeprazole (AUC ratio of 5-OH omeprazole to omeprazole) with GMRs of 9.35 (IM/PM) and 11.57 (EM/PM) after single dosing. These results were consistent with a previous study (31). With respect to the metabolic ratio omeprazole sulfone as mediated by *CYP3A4*, the GMR value of IM/PM after single dosing was 3.00 and significant. However, the GMR values of IM/PM and EM/PM after multiple dosing included 1 in 90% confidence interval, which implies that there were no significant differences in *CYP3A4* activity between PM and IM or EM. It therefore appears that the elevated $AUC_{0\rightarrow12hr}$ of omeprazole and the PD responses (change of mean pH and % time of gastric pH above 4.0) in the PM group were caused by lowered *CYP2C19* activity.

The *CYP2C19* PM group showed the greatest $AUC_{0\rightarrow12hr}$ for omeprazole (32-34) and the most pronounced effects on intragastric pH (35), as has also been reported in other studies. It has been shown that the degree of gastric acidity suppression correlates with omeprazole's AUC (26,36). Based on PK/PD relationship, increased AUC of omeprazole in the PM group would lead to increased probability of therapeutic success. On the other hands, it seemed to be weak of safety concerns according to *CYP2C19* phenotypes due to a wide therapeutic window of omeprazole (37). No omeprazole-related adverse event in the PM group was reported in this study. However, further studies are necessary in order to confirm the safety of omeprazole in the *CYP2C19* PM group.

After repeated administration for 8 days, the $AUC_{0\rightarrow12hr}$ values of omeprazole were higher in all 3 groups compared to those after single dosing. Reduced *CYP2C19* activity after multiple dosing appeared to lead to reduced first-pass elimination, as reported in a previous study (26). As the $AUC_{0\rightarrow12hr}$ of omeprazole increased in the context of repeated administration, the effect of omeprazole in lowering gastric pH was enhanced in all 3 groups. Compared to the metabolic ratios after single dosing, the differences in metabolic ratio of 5-OH omeprazole to omeprazole and in the gastric pH lowering effect among groups decreased in the context of repeated dosing. A possible reason for the smaller differences in metabolic ratio and pH lowering effect in the context of repeated dosing is inhibition of *CYP2C19* activity by omeprazole, as reported previously (38). Despite the fact that omeprazole is eliminated rapidly from plasma, the drug is still effective 24 to 72 hours after a single dose (36). Another possible reason for the smaller difference in pH lowering effect among the 3 groups in the context of repeated administration compared to single dosing is the long-lasting effect of omeprazole.

According to the Prilosec® label of Food and Drug Administration, a greater than linear response in AUC occurs with doses greater than 40 mg because of saturation of first-pass elimina-

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tion, while the AUC of omeprazole is known to be approximately proportional to doses up to 40 mg. This study showed that roughly half the dose of omeprazole in the PM group would probably correspond to the same omeprazole exposure as in the IM and EM groups, for doses of less than 40 mg (34). However, further study will be needed to evaluate the clinical necessity of genotype dose adjustment of omeprazole.

One limitation of this study is that the therapeutic effect of omeprazole could not be evaluated because the trial subjects were healthy volunteers. However, a positive relationship between % time of gastric pH above 4.0 and the possibility of GERD treatment has been reported (39), and one should be able to predict the therapeutic effects of omeprazole from gastric pH on the basis of this relationship. Along with the absence of a direct indicator of treatment effect, another possible limitation is that other factors that were not considered in this study may influence the PKs of omeprazole and gastric pH. Further studies will be needed to formulate quantitative dosing guidelines that consider factors apart from *CYP2C19* genotypes. Nevertheless, this study provides valuable evidence about the implications of *CYP2C19*2* and **3*, in the absence of **17* mutations, for single and multiple dose omeprazole treatment.

In conclusion, this study has confirmed that *CYP2C19*2* and **3* influence the PKs and PDs of omeprazole in Korean healthy volunteers. The relationship between the AUC of omeprazole and the change of mean pH was confirmed.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Hyun YJ, Kim JM, Kim YR, Na HS. Data curation: Kim YR, Lee JH, Oh J. Formal analysis: Oh J, Park S, Ryu S. Investigation: Park S, Ryu S, Kim JK, Oh WY, Na HS, Lee JG, Seo DW, Hwang IY, Park Z, Choi SE. Supervision: Choi SE, Kim JM, Jang IJ. Writing - original draft: Park S, Choi SE.

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REFERENCES

1. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology* 2010; 139: 1115-27.
2. Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics* 2011; 12: 873-88.
3. Chaudhry AS, Kochhar R, Kohli KK. Genetic polymorphism of *CYP2C19* & therapeutic response to proton pump inhibitors. *Indian J Med Res* 2008; 127: 521-30.
4. Simon B, Elsner H, Müller P. Protective effect of omeprazole against low-dose acetylsalicylic acid. Endoscopic controlled double-blind study in healthy subjects. *Arzneimittelforschung* 1995; 45: 701-3.
5. Karam WG, Goldstein JA, Lasker JM, Ghanayem BI. Human *CYP2C19* is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; 24: 1081-7.
6. Pearce RE, Rodrigues AD, Goldstein JA, Parkinson A. Identification of the human P450 enzymes involved in lansoprazole metabolism. *J Pharmacol Exp Ther* 1996; 277: 805-16.
7. VandenBranden M, Ring BJ, Binkley SN, Wrighton SA. Interaction of human liver cytochromes P450 in vitro with LY307640, a gastric proton pump inhibitor. *Pharmacogenetics* 1996; 6: 81-91.
8. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; 31: 9-28.
9. Meyer UA. Metabolic interactions of the proton-pump inhibitors lansoprazole, omeprazole and pantoprazole with other drugs. *Eur J Gastroenterol Hepatol* 1996; 8 Suppl 1: S21-5.
10. Andersson T, Lagerstrøm PO, Miners JO, Veronese ME, Weidolf L, Birkett DJ. High-performance liquid chromatographic assay for human liver microsomal omeprazole metabolism. *J Chromatogr* 1993; 619: 291-7.
11. Li XQ, Weidolf L, Simonsson R, Andersson TB. Enantiomer/enantiomer interactions between the S- and R- isomers of omeprazole in human cytochrome P450 enzymes: major role of *CYP2C19* and *CYP3A4*. *J Pharmacol Exp Ther* 2005; 315: 777-87.
12. Abelö A, Andersson TB, Antonsson M, Naudot AK, Skånberg I, Weidolf L. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos* 2000; 28: 966-72.
13. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999; 13 Suppl 3: 27-36.
14. Qiao HL, Hu YR, Tian X, Jia LJ, Gao N, Zhang LR, Guo YZ. Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the *CYP2C19* genotype. *Eur J Clin Pharmacol* 2006; 62: 107-12.
15. Hassan-Alin M, Andersson T, Niazi M, Röhss K. A pharmacokinetic study comparing single and repeated oral doses of 20 mg and 40 mg omeprazole and its two optical isomers, S-omeprazole (esomeprazole) and R-omeprazole, in healthy subjects. *Eur J Clin Pharmacol* 2005; 60: 779-84.
16. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Büttner HJ, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous cor-

onary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008; 51: 1925-34.
17. Collet JP, Hulot JS, Pena AN, Villard ER, Esteve JB, Cayla G, Silvain G, Beygui F, Payot L, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: impact on clinical events and on. *Eur Heart J* 2009; 30: 906.
18. Jeong YH, Kim IS, Kwak CH, Hwang JY. AS-192: the *CYP2C19*2* and *CYP2C19*3* polymorphisms are associated with high posttreatment platelet reactivity in patients with acute myocardial infarction. *Am J Cardiol* 2009; 103: 82B.
19. Kim IS, Choi BR, Jeong YH, Kwak CH, Kim S. The *CYP2C19*2* and *CYP2C19*3* polymorphisms are associated with high post-treatment platelet reactivity in Asian patients with acute coronary syndrome. *J Thromb Haemost* 2009; 7: 897-9.
20. Marcucci R, Giusti B, Gori A, Paniccia R, Saracini C, Vestrini A, Nanna C, Cordisco A, Antonucci E, Gensini G, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients are predicted by residual platelet reactivity to ADP in the absence of *CYP2C19*2* allele: beyond genetic screening. *J Thromb Haemost* 2009; 7: 91.
21. Bonello L, Armero S, Ait Mokhtar O, Mancini J, Aldebert P, Saut N, Bonello N, Barragan P, Arques S, Giacomoni MP, et al. Clopidogrel loading dose adjustment according to platelet reactivity monitoring in patients carrying the 2C19*2 loss of function polymorphism. *J Am Coll Cardiol* 2010; 56: 1630-6.
22. Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L, Ingelman-Sundberg M. A common novel *CYP2C19* gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther* 2006; 79: 103-13.
23. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, van Schaik RH, Schalekamp T, Touw DJ, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther* 2011; 89: 662-73.
24. Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L, Kobayakawa T, Björkman A. High and variable frequencies of *CYP2C19* mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics* 1999; 9: 581-90.
25. Prichard PJ, Yeomans ND, Mihaly GW, Jones DB, Buckle PJ, Smallwood RA, Louis WJ. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. *Gastroenterology* 1985; 88: 64-9.
26. Andersson T, Cederberg C, Regårdh CG, Skånberg I. Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol* 1990; 39: 195-7.
27. Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; 40: 411-26.
28. Hofmann U, Schwab M, Treiber G, Klotz U. Sensitive quantification of omeprazole and its metabolites in human plasma by liquid chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006; 831: 85-90.
29. Shimizu M, Uno T, Niioka T, Yaui-Furukori N, Takahata T, Sugawara K, Tateishi T. Sensitive determination of omeprazole and its two main metabolites in human plasma by column-switching high-performance liquid chromatography: application to pharmacokinetic study in relation to *CYP2C19* genotypes. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006; 832: 241-8.
30. Bedada W, de Andrés F, Engidawork E, Pohanka A, Beck O, Bertilsson L, Llerena A, Aklillu E. The psychostimulant Khat (Catha edulis) inhibits CYP2D6 enzyme activity in humans. *J Clin Psychopharmacol* 2015; 35: 694-9.
31. Sagar M, Seensalu R, Tybring G, Dahl ML, Bertilsson L. *CYP2C19* genotype and phenotype determined with omeprazole in patients with acid-related disorders with and without *Helicobacter pylori* infection. *Scand J Gastroenterol* 1998; 33: 1034-8.
32. Furuta T, Ohashi K, Kosuge K, Zhao XJ, Takashima M, Kimura M, Nishimoto M, Hanai H, Kaneko E, Ishizaki T. *CYP2C19* genotype status and effect of omeprazole on intragastric pH in humans. *Clin Pharmacol Ther* 1999; 65: 552-61.
33. Jin SK, Kang TS, Eom SO, Kim JI, Lee HJ, Roh J. *CYP2C19* haplotypes in Koreans as a marker of enzyme activity evaluated with omeprazole. *J Clin Pharm Ther* 2009; 34: 437-46.
34. Cho JY, Yu KS, Jang IJ, Yang BH, Shin SG, Yim DS. Omeprazole hydroxylation is inhibited by a single dose of moclobemide in homozygotic EM genotype for *CYP2C19*. *Br J Clin Pharmacol* 2002; 53: 393-7.
35. Sagar M, Tybring G, Dahl ML, Bertilsson L, Seensalu R. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the *CYP2C19* polymorphism. *Gastroenterology* 2000; 119: 670-6.
36. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. *Gut* 1983; 24: 270-6.
37. Andersson T, Regårdh CG. Pharmacokinetics of omeprazole and metabolites following single intravenous and oral doses of 40 and 80mg. *Drug Investig* 1990; 2: 255-63.
38. Zhou Q, Yamamoto I, Fukuda T, Ohno M, Sumida A, Azuma J. *CYP2C19* genotypes and omeprazole metabolism after single and repeated dosing when combined with clarithromycin. *Eur J Clin Pharmacol* 1999; 55: 43-7.
39. Armstrong D. Review article: gastric pH -- the most relevant predictor of benefit in reflux disease? *Aliment Pharmacol Ther* 2004; 20 Suppl 5: 19-26.

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