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

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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-de-methylomeprazole, 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
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 on 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
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 r² > 0.99 for the 3 compounds. The lower limit of quantification (LLOQ) was 5 ng/mL for all analytes.

**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→12h}) and the area under the concentration time curve from 0 to infinity (AUC_{\infty}). 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

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

| SNP   | Rs number    | Variation | Sequence (5’-3’) |
|-------|--------------|-----------|------------------|
| CYP2C19*2 | rs4244285    | 681G>A    | CAACCAAGCTTGCAATTTG |
|        | Forward primer |           | CAAATACGCAAGTCACA |
|        | Reverse primer |           | TCTTAGATAGCAATATCTTCC |
| CYP2C19*3 | rs4986893    | 636G>A    | CCGCGTTGACACTTTCT |
|        | Forward primer |           | ATTCACCCCATGGCTGTCTA |
|        | Reverse primer |           | AAAACATCAAGTATTAGAGCACCCCTG |
| CYP2C19*17 | rs12248560   | −806C>T   | GCAGTGATGGGAAAGAG |
|         | Forward primer |           | GAAGCTGGGAGAACTGGATT |
|         | Reverse primer |           | TTTTTTTTTTCAATTGTCTCTCGTCTCAAG |

SNP = single nucleotide polymorphism.
Kruskal-Wallis 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 consent was obtained from all patients.
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/m². 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 AUC₀→12hr values of omeprazole, metabolic ratios 5-OH omeprazole (AUC₀→12hr, 5-OH omeprazole/omeprazole) after single and multiple dosing, and the GMRs of the metabolic ratios. The AUC₀→12hr 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 AUC₀→12hr of omeprazole increased after repeated administration. The metabolic ratio omeprazole sulfone (AUC₀→12hr, 5-OH omeprazole sulfone/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 AUC₀→12hr 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 |            |            |            |             |             |
| AUC₀→12hr, 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 |            |            |            |             |             |
| AUC₀→12hr, 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 | 0.39 (0.59–1.66) | 1.46 (0.87–2.46) |

The metabolic ratio and AUC₀→12hr values (µg × hr/L) are given as mean ± standard deviation. GMR values report the geometric mean ratio and 90% confidence interval. AUC₀→12hr = area under the concentration time curve from 0 to 12 hour after dosing, AUC₀→12hr, omeprazole = AUC₀→12hr of omeprazole, AUC₀→12hr, 5-OH omeprazole = AUC₀→12hr of 5-hydroxy omeprazole, AUC₀→12hr, omeprazole sulfone = AUC₀→12hr of omeprazole sulfone, PM = poor metabolizer, IM = internal medicine, EM = emergency medicine, GMR = geometric mean ratio, Metabolic ratio 5-OH omeprazole = AUC₀→12hr, 5-OH omeprazole/AUC₀→12hr, omeprazole, Metabolic ratio omeprazole sulfone = AUC₀→12hr, omeprazole sulfone/AUC₀→12hr, omeprazole.
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        |             |             |             |          |
| 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      |             |             |             |          |
| 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-Wallis test.

Omeprazole AUC∞ 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∞ 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∞ 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∞ of omeprazole (32-34) and the most pronounced effects on intra-gastric 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 hand, 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∞ 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∞ 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-
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 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 IV, Park Z, Choi SE. Supervision: Choi SE, Kim JM, Jang II. Writing - original draft: Park S, Choi SE.

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