CYP2C19 Genotype Related Effect of Omeprazole on Intragastric pH and Antimicrobial Stability

Tomoko Kita,[1] Yusuke Tanigawara,[1,3] Nobuo Aoyama,[2] Takashi Hohda,[1] Yoshie Saijoh,[1] Fusao Komada,[1,4] Toshiyuki Sakaeda,[1] Katsuhiko Okumura,[1,5] Toshiyuki Sakai,[2] and Masato Kasuga[2]

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Purpose. A combination of proton pump inhibitors and antimicrobials has been applied as an anti-*Helicobacter pylori* (*H. pylori*) therapy. Omeprazole, one of the proton pump inhibitors, is metabolized by CYP2C19, which exhibits genetic polymorphism. It was reported previously that the overall anti-*H. pylori* efficacy can be related to the *CYP2C19* genotype. The main aim of the present study was to obtain a rational explanation for the relationship between the overall anti-*H. pylori* efficacy and the *CYP2C19* genotype.

Methods. Six healthy volunteers were classified as extensive metabolizers and poor metabolizers, according to their *CYP2C19* genotypes. Plasma concentrations and intragastric pH were monitored prior to and until 24 h after the administration of 20 mg omeprazole. The stability of amoxicillin, clarithromycin, and metronidazole was examined using buffer solutions with monitored intragastric pH, and their remaining percentage in the intragastric space was simulated.

Results. The poor metabolizers, classified by the *CYP2C19* genotypes, showed the higher effectiveness in anti-*H. pylori* therapy, via the higher plasma concentration of omeprazole and the higher intragastric pH, and possibly the higher stability of antimicrobials in the higher intragastric pH.

Conclusions. *CYP2C19* genotyping is a very useful method to determine the effective and safe dosage regimen including the selection of the dual and triple therapy in anti-*H. pylori* therapy.

KEY WORDS: CYP2C19; genotype; omeprazole; *Helicobacter pylori*; intragastric pH; stability of antimicrobials.

INTRODUCTION

One of major problems in pharmacotherapy is the interindividual variability of efficacy and toxicity using the same dosage regimen. Because the efficacy or toxicity is defined by the pharmacokinetic and pharmacodynamic properties of drugs, therapeutic drug monitoring, or the checking of blood concentrations of drugs, is now used world-wide in medicinal therapy to overcome interindividual variability of pharmacokinetics and to allow tailor-made dosage regimens for each patient.

Recently, a number of investigations in pharmacogenomics have suggested that the interindividual variability can be attributed to drug metabolizing enzymes which exhibit polymorphism, including N-acetyltransferase and several cytochrome P450 isoforms (1). CYP2C19 is one of the cytochrome P450 isoforms and catalyzes S-mephenytoin, omeprazole, lansoprazole, imipramine and diazepam (2). Approximately 2–5% of Caucasians and 13–23% of Asians are known to be deficient in the ability to metabolize via CYP2C19, which was found by phenotyping (3,4). De Morais *et al.* reported that the two principal genetic defects responsible for the poor metabolizer phenotype in Japanese subjects are a single base-pair mutation (G →A) in exon 5 (*CYP2C19*2*) and exon 4 (*CYP2C19*3*) of the *CYP2C19* gene (5,6). The phenotype patterns of Japanese poor metabolizers can be almost perfectly explained by homozygote for *CYP2C19*2* (*CYP2C19*2/CYP2C19*2*), *CYP2C19*3* (*CYP2C19*3/CYP2C19*3*) and compound heterozygote for these two defects (*CYP2C19*2/CYP2C19*3*) (6–8). Since 1988 (9), the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method has been developed, which allows assessment of the genetic polymorphisms within a short time (5,6,10).

Omeprazole, a substituted benzimidazole derivative, suppresses gastric acid secretion by inhibition of the H^+, K^+-ATPase, proton pump, in the gastric parietal cells (11), and is used in the treatment of duodenal and gastric ulcer, Zollinger—Ellison syndrome, and other related hyperacidic conditions (11). Recently, omeprazole was also used in the therapy for eradicating *Helicobacter pylori* (*H. pylori*) with antimicrobials such as amoxicillin, clarithromycin and metronidazole (12–17), resulting in the reduction of gastric and duodenal ulcer diseases (12,13). Omeprazole increases the intragastric pH, and the susceptibility of *H. pylori* to antimicrobials (18,19), the growth inhibition of *H. pylori* (20), the secretion of antimicrobials to the gastric space (21,22) and the stability of antimicrobials (23) are reported to depend on the pH. Omeprazole is catalyzed mainly by CYP2C19 with only minor contribution of CYP3A4 and others (24). We previously demonstrated that anti-*H. pylori* efficacy after the combination treatments consisting of omeprazole and amoxicillin (dual therapy) or of omeprazole, amoxicillin and clarithromycin (triple therapy), depended on the genetic differences in the *CYP2C19* gene, and in addition, that the efficacy of the combination with nizatigine/famotidine, metronidazole, amoxicillin and bismuth subnitrate was not related to the *CYP2C19* genotype (25,26). Furuta et al. also has reported the effect of the genetic differences in omeprazole metabolism on cure rates by omeprazole and amoxicillin for *H. pylori* infection and peptic ulcer (27).

In the present study, the time-profiles of the plasma concentrations of omeprazole and its two metabolites (5-hydroxyomeprazole and omeprazole sulfone), and the intragastric pH were monitored after administration of omeprazole to extensive and poor metabolizers defined by *CYP2C19* genotyping. The stability of amoxicillin, clarithromycin and metronidazole on the monitored intragastric pH was also assessed, to figure out the rational explanation for the relation-

[1] Department of Hospital Pharmacy, School of Medicine, Kobe University, Chuo-ku, Kobe 650-0017, Japan.
[2] Second Department of Internal Medicine, School of Medicine, Kobe University, Chuo-ku, Kobe 650-0017, Japan.
[3] Current address: Department of Hospital Pharmacy, School of Medicine, Keio University, Shinjuku-ku, Tokyo 160-8582, Japan.
[4] Current address: Department of Drug Informatics, Faculty of Pharmaceutical Sciences, Josai University, Keyakidai Sakado, Saitama 350-0290, Japan.
[5] To whom correspondence should be addressed (e-mail: okumurak@kobe-u.ac.jp)

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ship between the *CYP2C19* genotype and the anti-*H. pylori* efficacy.

MATERIALS AND METHODS

Chemicals

Omeprazole and its two metabolites were obtained from AstraZeneca Ltd. (Osaka, Japan). Amoxicillin and metronidazole were purchased from Sigma Chemical Co. (Poole, UK). Clarithromycin was obtained from Taisho Pharmaceuticals (Osaka, Japan). All other chemicals were of reagent grade and obtained commercially.

Subjects

Six healthy male volunteers participated in this study. The mean age was 25.5 years old (range 23–32 years), and the mean body weight was 54.5 kg (range 50–60 kg). None had a history of peptic ulcer disease, nor serum positive-*H. pylori* antibody. Prior to entry to the study, informed written consent was obtained from each subject. The following study protocol, including *CYP2C19* genotyping and plasma concentration and intragastric pH monitoring, was approved by the ethics committees of the School of Medicine, Kobe University, Japan.

CYP2C19 Genotyping by the PCR-RFLP Method

CYP2C19 genotyping from peripheral blood samples were performed by the PCR-RFLP method (5,6). Briefly, two milliliters of heparinized blood was obtained and genomic DNA was extracted with a DNA Extractor WB Kit (Wako Pure Chemical Industries Ltd., Osaka, Japan). The wild-type *CYP2C19*1* gene and the two mutated genes, *CYP2C19*2* and *CYP2C19*3* were identified by PCR amplification using the allele-specific primers, which were synthesized by Rikaken Co. (Nagoya, Japan), namely m1F (5′-AATTACAACCAGAGCTTGGC-3′), m1R (5′-TATCACTTTCCATAAAAGCAAG-3′), m2F (5′-ATTGAATGAAAACATCAGGATTG-3′), and m2R (5′-ACTTCAGGGCTTGGTCAA-TA-3′). The 169-bp and 130-bp sequences of the *CYP2C19* gene were amplified by PCR with a pair of the oligonucleotide primers and a Gene Amp PCR Reagent Kit (Takara Shuzo Co., Kyoto, Japan). The DNA (approximately 500 ng) was amplified by 30 PCR cycles. The conditions were 3 min at 94°C, 2 min at 55°C, and 3 min at 72°C for the first cycle, followed by 28 cycles of 1 min at 94°C, 0.5 min at 55°C, and 0.4 min at 72°C. The following final period was 1 min at 94°C, 0.5 min at 55°C, and 10 min at 72°C. The temperature was controlled by a programmable heat block (Program Temp Control System PC-700, Astec Co., Fukuoka, Japan). After amplification, the PCR product was taken directly from the aqueous phase, and was digested with restriction endonucleases, *Sma* I or *Bam* HI (Takara Shuzo Co.), in the appropriate basal buffer. The fragments digested by these enzymes were separated by 3% agarose gel electrophoresis, along with a DNA molecular weight marker (pUC18 *Hae* III Digest, Sigma Chemical Co. St. Louis, MO) for reference.

Time-Profiles of Plasma Concentrations of Omeprazole and Its Metabolites and Intragastric pH After Oral Administration of Omeprazole

Time-profiles of plasma concentrations of omeprazole and its metabolites (5-hydroxyomeprazole and omeprazole sulfone) and intragastric pH were monitored after oral administration of omeprazole to six healthy male volunteers stratified based on the *CYP2C19* genotype. This study consisted of period I and period II with a time interval of 1 week, and the subjects were restricted for 24 h from 09:00 h to 09:00 h on the next day for periods I and II. Regular meals were provided at 08:30, 12:00, and 20:30 h. Extra snacks and beverages and smoking were prohibited. Subjects were allowed to rest from 24:00 h to 07:00 h on the next day. During period I, there was no administration of omeprazole, and only the intragastric pH was monitored. During period II, 20 mg of omeprazole was orally administered twice a day as enteric-coated tablets (AstraZeneca Ltd.) at 09:00 h and 21:00 h followed by plasma concentration and intragastric pH monitoring.

Blood samples, 5 ml each, were collected from the cephalic vein on the forearm for determination of the plasma concentration of omeprazole and its two metabolites only at 09:00 for period I and at 09:00, 10:00, 11:00, 12:00, 13:00, 15:00, and 21:00 h for period II. Plasma was separated quickly and was stored at −85°C until measurement. The plasma concentrations of omeprazole and its two metabolites were determined by reverse phase HPLC, basically according to the report by Kobayashi (28). One-hundred microliters 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 1,500 × 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. The residue was then dissolved in 300 μl of the mobile phase and filtered using a 0.2-μm filter (HPLC Sample Prep LCR4-LG, Nihon Millipore Ltd., Tokyo). Fifty-microliter aliquots were injected into the high-performance liquid chromatography (HPLC) system consisting of an LC-6A pump, SPD-6AV detector, CTO-6A column oven (at 40°C), SCL-6B system controller, and C-R4A chromatopak (Shimadzu Co., Kyoto, Japan). A CAPCELL PAK C18 SG 120 column (particle size 5 μm, 350 mm × 4.6 mm I.D., Shiseido Co., Tokyo, Japan) and acetonitrile-0.05 M phosphate buffer (pH 8.5) (25:75, v/v) were used as the column and mobile phase, respectively. The flow rate was 0.8 ml/min, and detection wavelength was 302 nm. Their limit in quantification was 10 ng/ml.

Intragastric pH was simultaneously monitored for both periods I and II. The basal findings were from period I, and the effect of omeprazole was from Period II. Intragastric pH was monitored using miniature glass electrodes (CM151B, Chemical Kiki Co., Tokyo, Japan) connected to a portable pH recorder (CR5501, Chemical Kiki Co.), which records pH levels every 10 s and stores it in a built-in solid-state memory and subsequently integrates into the 5-min mean pH. The electrode was inserted into the stomach nasally, and the tips of the electrodes were positioned at the middle of the gastric corpus under fluoroscopic control. A reference electrode was placed on the right anterior chest wall. The electrode was calibrated at 25°C with commercial buffers (pH 1.68, 4.01 and

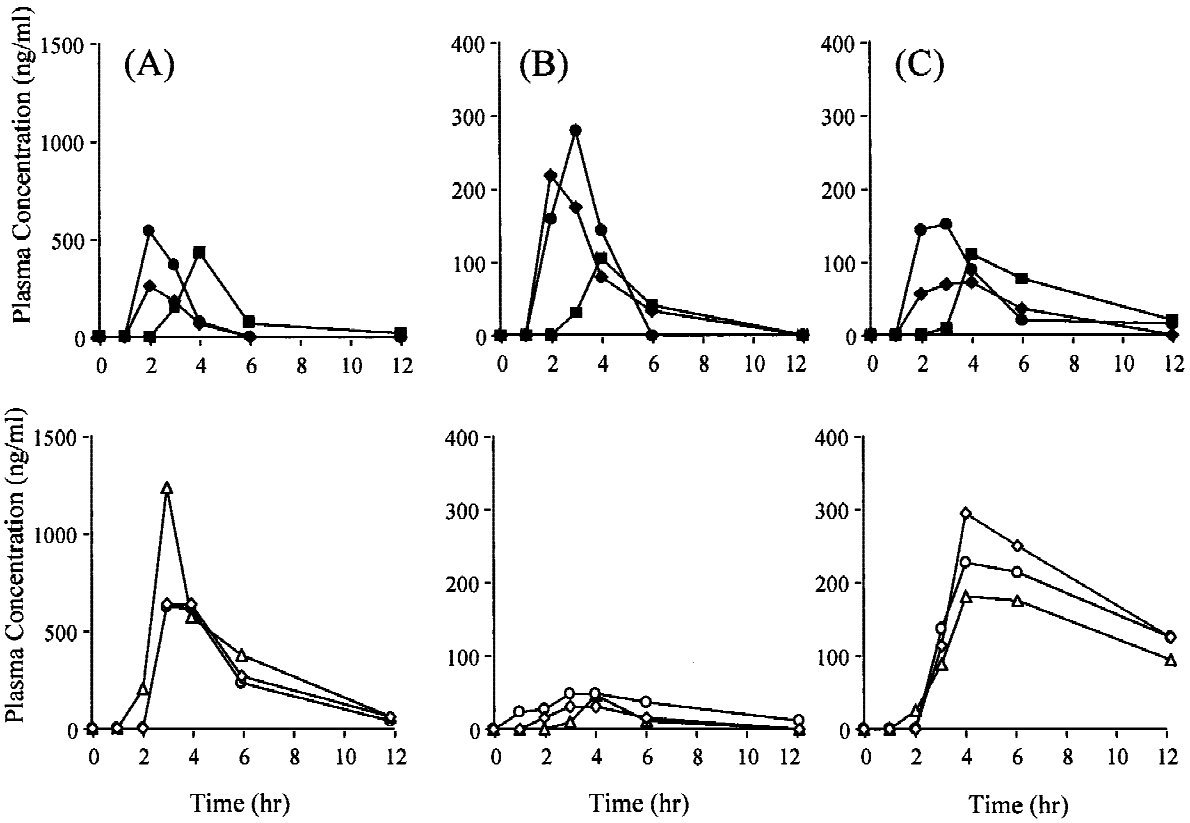

Fig. 1. Time-profiles of (A) omeprazole, (B) 5-hydroxy omeprazole, and (C) omeprazole sulfone in three extensive metabolizers (subject no. 1 ■, No. 2 ◆, No. 3 ●) and three poor metabolizers (subject no. 4 △, No. 5 ◇, No. 6 ○).

6.86, Wako Pure Chemical Industries, Ltd.) at the start and at the end of periods I and II, and a correction for 37°C was performed.

Data Analysis

Their peak concentrations (C_{max}) were taken directly from the measurements. The area under the plasma concentration-time curve (AUC) of omeprazole and its two metabolites were calculated by the linear trapezoidal method until 24 h. Statistical analyses were performed using by non-paired *t* test to compare these values between extensive and poor metabolizers defined by the *CYP2C19* genotyping. The anti-acid secretory effect of omeprazole was assessed by the overall mean of intragastric pH and the percentage of the time with intragastric pH >4 or 6 (29,30). Because of the nature of skewness of the pH distribution among subjects, a non-parametric Mann–Whitney method was used for statistical analysis. In all cases, the criterion for statistical significance was $P < 0.05$.

In Vitro Stability of Amoxicillin, Clarithromycin, and Metronidazole

The *in vitro* stability of amoxicillin, clarithromycin, and metronidazole in 0.02 M phosphate buffers adjusted to pH 1.2, 3.0, 4.0, and 6.0 with 1 M HCl or 1 M NaOH was investigated at 37°C according to Erah *et al.* (23). The concentrations in the buffered solutions were determined using a reverse-phase HPLC system including an LC-10AT pump, SPD-10A detector, CTO-10A column oven, SCL-10A system controller, and C-R7A chromatopak (Shimadzu Co.). A HYPERSIL ODS column (particle size 5 μm, 150 mm× 4.6 mm I.D., Chemco Co., Osaka, Japan) was used and the flow rate was fixed as 1.0 ml/min. The mobile phase consisted of a methanol 0.05 M phosphate buffer (pH 3.0) containing 0.1% triethylamine (5:95, v/v), acetonitrile 0.05 M phosphate buffer (pH 4.6) containing 5 mM octane sulfonic acid (53:47, v/v), and an acetonitrile 0.05 M phosphate buffer (pH 7.0) containing 0.1% triethylamine (13:87, v/v), respectively. Column temperatures were 40°C, 50°C, and 40°C, and the detection wavelengths were 230 nm, 210 nm, and 317 nm, respectively.

Time-profiles of the remaining quantities of each antimi-

Table I. Pharmacokinetic Parameters of Omeprazole and Its Two Metabolites in Extensive and Poor Metabolizers[a]

	Extensive metabolizers		Poor metabolizers	
CYP2C19 genotype	C_{max} (ng/ml)	AUC_{0-24} (ng · h/ml)	C_{max} (ng/ml)	AUC_{0-24} (ng · h/ml)
Omeprazole	412 ± 140	895 ± 312	811 ± 343	3054 ± 720*
5-Hydroxy omeprazole	201 ± 88	545 ± 173	41 ± 9**	206 ± 121**
Omeprazole sulfone	110 ± 40	485 ± 97	230 ± 56*	1634 ± 276**

[a] Each value represents the mean ± SD of three subjects. *$P < 0.05$, **$P < 0.01$: significantly different from extensive metabolizers defined by *CYP2C19* genotyping.

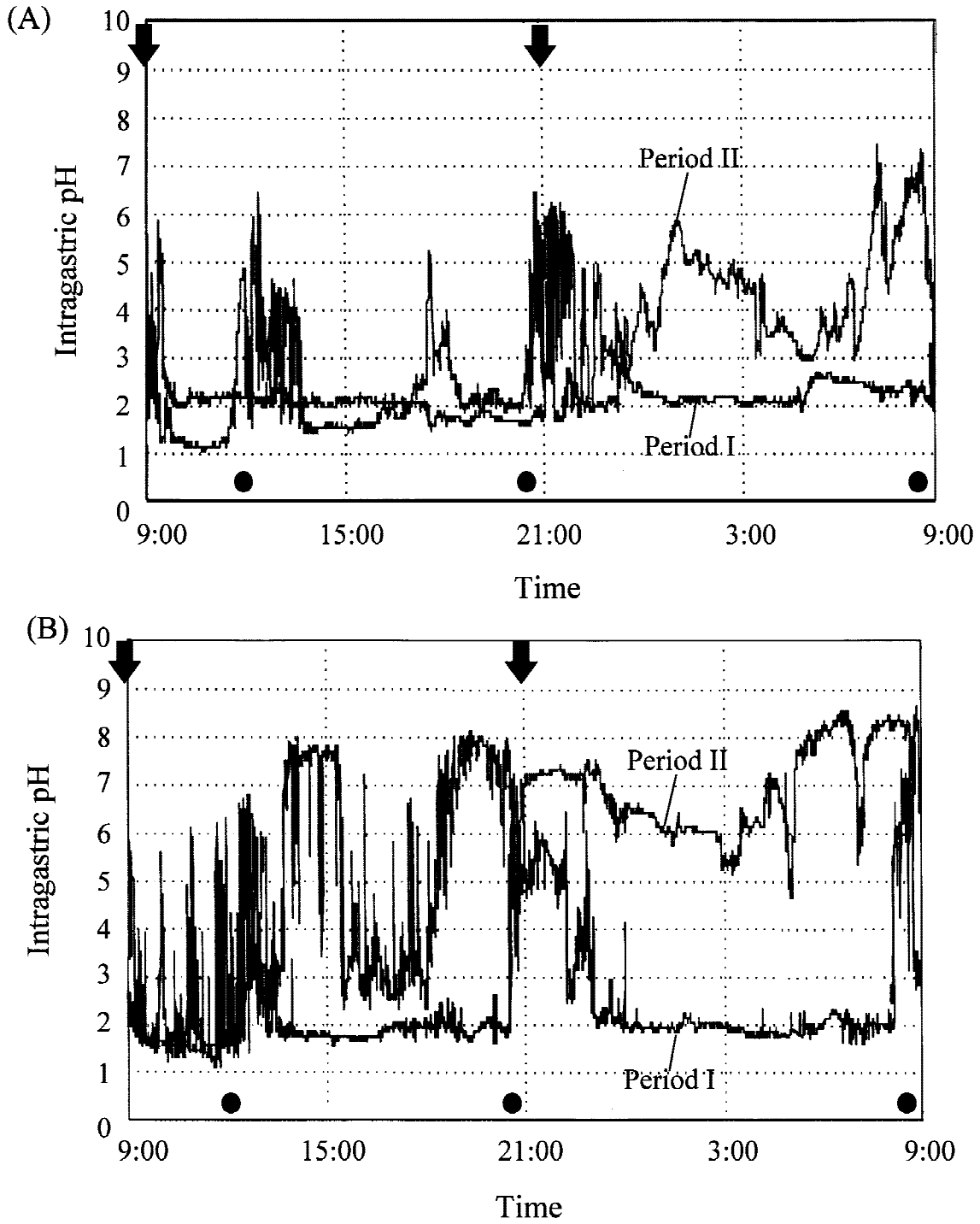

Fig. 2. Time-profiles of Intragastric pH for period I (no administration of omeprazole) and II (oral administration of omeprazole) in subject no. 2 (extensive metabolizer) (A) and Subject no. 4 (poor metabolizer) (B). ↓: omeprazole administration (20 mg twice a day) for Period II, ●: meal.

crobial was analyzed using the pseudo first-order equation: $X_t = X_0 \times e^{-kt}$, where X_0 and X_t are the remaining amounts of each antimicrobial at time zero and t (h), respectively, and k (h^{-1}) is the pseudo first-order degradation rate constant. The 24-h time profile of intragastric pH of each healthy subject was smoothed out every one hour using a portable pH recorder (CR5501, Chemical Kiki Co.), and the time course of antimicrobials remaining in the intragastric space was simulated according to each intragastric pH profile. The degradation rate constant at each pH was estimated using the experimentally obtained k values at pH 1.2, 3.0, 4.0, and 6.0. Each antimicrobial was added four times at 09:00, 12:00, 18:00 and 21:00 hr, and this time schedule was based on our anti-*H. pylori* therapy.

Table II. Overall Mean of Intragastric pH and the Percentage of the Time with Intragastric pH > 4 or 6 During Periods I or II in the Extensive and Poor Metabolizers[a]

Period *CYP2C19* genotype	Overall mean of intragastric pH	pH > 4 (%)[a]	pH > 6 (%)[b]
I (no administration)			
Extensive metabolizers	2.4 ± 0.4	7.2 ± 5.4	0.9 ± 1.1
Poor metabolizers	2.4 ± 0.6	8.3 ± 2.4	2.3 ± 2.5
II (omeprazole administration)			
Extensive metabolizers	3.4 ± 0.8	36.7 ± 10.8	8.0 ± 7.8
Poor metabolizers	5.1 ± 0.5[c]	72.3 ± 2.9[c]	36.0 ± 18.4

[a] Each value represents the mean ± SD of three subjects.
[b] Values are presented as the percentage of the time with intragastric pH > 4 or 6 (for 24 hr).
[c] $P < 0.05$: significantly different from extensive metabolizers defined by *CYP2C19* genotyping.

RESULTS

Time-Profiles of Plasma Concentrations of Omeprazole and Its Metabolites After Oral Administration of Omeprazole

Based on the *CYP2C19* genotype, six subjects were classified to either extensive metabolizers [*CYP2C19*1/CYP2C19*1* (subject no.1) and *CYP2C19*1/CYP2C19*2* (subjects no. 2, 3)] or poor metabolizers [*CYP2C19*2/CYP2C19*2* (subjects no. 4, 5) and *CYP2C19*3/CYP2C19*3* (subject no. 6)]. The plasma concentration-time curves of omeprazole and its two metabolites in each subject who took omeprazole 20 mg are shown in Figure 1, and the pharmacokinetic parameters are in Table I. Although the peak plasma concentration of omeprazole was observed 2–4 h after administration in all subjects, C_{max} and AUC were 2.0- and 3.4-fold higher in poor metabolizers than those in extensive metabolizers, respectively. The 5-hydroxyomeprazole/omeprazole AUC ratio was more than 9-fold lower in poor metabolizers than in extensive metabolizers, whereas the omeprazole sulfone/omeprazole AUC ratio was similar in extensive and poor metabolizers, reflecting the different contribution of CYP2C19 and CYP3A4 in the metabolic pathway.

Time-Profiles of Intragastric pH After Oral Administration of Omeprazole

Typical profiles of intragastric pH for period I (no administration of omeprazole) and II (oral administration of omeprazole) in the extensive metabolizer (subject no. 2) and poor metabolizer (subject no. 4) are shown in Figure 2, A and B, respectively. In the case of the extensive metabolizer, the intragastric pH was kept pH 2 for period I, and it rose from pH 1.2 (t = 09:00 h to 12:00 hr) to pH 4 (t = 12:00 h to 14:00 hr) with fluctuation, and was restored immediately to pH 1.2 (t = 14:00 h to 17:00 h) for period II. The intragastric pH in the poor metabolizer was maintained at pH 2, rising to pH 7, 3, and 5 at lunch, dinner, and breakfast respectively for period I. For period II, in contrast to the extensive metabolizer, it was maintained at pH 3 for the first 3 hr (t = 09:00 h to 12:00 h) with fluctuation, followed by an increase to around pH 6 for 3 h (t = 12:00 hr to 15:00 h) and around pH 4 for 2 h (t = 15:00 hr to 17:00 h) in the poor metabolizer.

Table II lists the overall mean intragastric pH and the percentage of the time with intragastric pH >4 or 6. The overall mean intragastric pH and the percentage of the time with intragastric pH >4 were significantly higher and longer in poor metabolizers compared with extensive metabolizers, respectively, whereas there was no difference in the basal pH.

In Vitro stability of Amoxicillin, Clarithromycin, and Metronidazole

The amoxicillin, clarithromycin and metronidazole in phosphate buffers with pH 1.2, 3.0, 4.0, and 6.0 were degraded with pseudo first-order kinetics (Table III). Amoxicillin was unstable only at pH 1.2 with a degradation half-life of 6.6 hr, and stability at pH 3.0, 4.0 and 6.0. Clarithromycin was extensively degraded at pH 1.2 and 3.0. In contrast, metronidazole was stable at the pH range studied.

The time-profiles of the remaining percentage of amoxicillin, clarithromycin and metronidazole were simulated according to the intragastric pH profiles for each subject (Figure 3. The findings were presented as the percentage of one dose. Amoxicillin remained in all subjects except for one extensive metabolizer reflecting relatively lower pH (0.25–0.35) than others (pH >0.6) at 16:00-21:00 h. The remaining percentage of clarithromycin was 41%, 139%, and 215% at 24 h in the extensive metabolizers, whereas it was 280%, 272%, and 273% in the poor metabolizers. In contrast, administered metronidazole remained in all subjects.

DISCUSSION

For anti-*H. pylori* therapy, dual therapy with omeprazole and amoxicillin was generally used until 1995, and the eradication rate has extensively varied significantly from 29% to 92% (12,14–16). Triple therapy with omeprazole, amoxicillin

Table III. Degradation Rate Constants of Amoxicillin, Clarithromycin, and Metronidazole at 37°C in Phosphate Buffer[a]

	k (h^{-1})		
pH	Amoxicillin	Clarithromycin	Metronidazole
1.2	0.105 ± 0.012	4.188 ± 0.097	0.004 ± 0.002
3.0	0.007 ± 0.002	0.045 ± 0.024	0.004 ± 0.002
4.0	0.002 ± 0.002	0.001 ± 0.001	0.005 ± 0.004
6.0	0.003 ± 0.001	0.004 ± 0.0003	0.001 ± 0.001

[a] Each value represents the mean ± SD of three experiments.

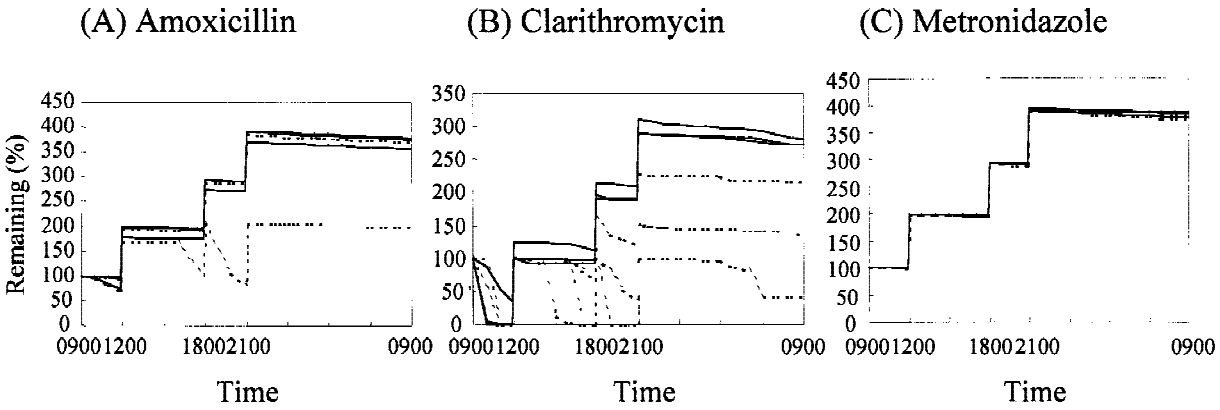

Fig. 3. Simulation curves of the remaining percentage of (A) amoxicillin, (B) clarithromycin, and (C) metronidazole according to the intragastric pH profiles in three extensive metabolizers (dotted line) and three poor metabolizers (solid line).

and clarithromycin/metronidazole is now recommended because of the high eradication rate (greater than 90%) (13,15,17); however, some problems have arisen using this therapy including the resistance of *H. pylori* to antimicrobials except for amoxicillin (13,16,31). Omeprazole is a key drug for anti-*H. pylori* therapy (13); however, it is still impossible to determine the effective and safe dosage regimen including the selection of dual or triple therapy. A series of studies has been conducted to allow tailor made dosage regimens for each subject, and the application of *CYP2C19* genotyping was proposed because omeprazole is metabolized mainly by polymorphic CYP2C19.

In our previous study, in the dual therapy with omeprazole (20 mg × 2 per day for 1 week) and amoxicillin (500 mg × 4 per day for 1 week), the eradication rate was 41% and 100% in the extensive and poor metabolizers, respectively. In the triple therapy using omeprazole (20 mg × 2 per day for 1 week), amoxicillin (500 mg × 4 per day for 1 week) and clarithromycin (200 mg × 4 per day for 1 week), the eradication rate was 83% and 100%, respectively (25,26). A possible explanation is that the antiacid secretion of omeprazole is expected to be more potent in poor metabolizers than in extensive metabolizers because of the longer AUC of omeprazole. The present study was performed to ascertain the rational explanation for the relationship between the *CYP2C19* genotype and the anti-*H. pylori* efficacy.

In the present study, the systemic exposure of omeprazole in poor metabolizers was markedly greater than that in extensive metabolizers as classified by the *CYP2C19* genotype. Among three extensive metabolizers, homozygote for *CYP2C19*1* (n = 1) showed the highest AUC of omeprazole. Further investigation will elucidate the pharmacokinetic difference between homozygote and compound heterozygote for *CYP2C19*1*. Although there was interindividual variability in the intragastric pH, the overall mean of intragastric pH and the percentage of the time with intragastric pH >4 or 6 in poor metabolizers were significantly higher than in extensive metabolizers during omeprazole dosing.

The susceptibility of several clinical isolates of *H. pylori* to antimicrobials was evaluated under various pH's, and the minimal inhibitory concentrations of amoxicillin and clarithromycin were found to increase significantly from 10- to 100-fold when the pH decreased from 7.0–7.9 to 5.5–5.75. The effect of intragastric pH on the susceptibility of *H. pylori* to antimicrobials could be explained by the dependence of antimicrobials permeability into the *H. pylori* on pH (21). The increase in the secretion of antimicrobials to the gastric space when omeprazole was co-administered was also suggested (21,22). In addition, Erah et al. reported that the stability of antimicrobials depended on the pH 1.0–8.0 (23). These factors can be important for anti-*H. pylori* therapy, however, their contributions have not been clarified. Here, we simulated the time-profiles of the remaining percentage of antimicrobials in the intragastric space by use of their degradation rate constant. Although the remaining of antimicrobials can be altered by the gastric emptying and by their absorption from the stomach and intestines, the amoxicillin and clarithromycin in poor metabolizers was estimated to be more remained than in extensive metabolizers.

It was suggested that the mean of intragastric pH (28) and also the stability of antimicrobials might determine the success or failure of the anti-*H. pylori* therapy. These findings provide an explanation for the interindividual variability in the efficacy of the anti-*H. pylori* therapy with omeprazole and antimicrobials, and will provide effective and safe dosage regimens in the anti-*H. pylori* therapy. In general, it has been empirically recommended to increase the dose of omeprazole or amoxicillin to ensure a higher eradication rate during dual therapy (16). However, the present study has suggested that an increase in the amoxicillin dose would not necessarily result in higher effectiveness. Alternatively, it is suggested to use the *CYP2C19* genotyping in the anti-*H. pylori* therapy. When patients are diagnosed as poor metabolizers, the dual therapy with omeprazole and amoxicillin will be enough, and neither increase of amoxicillin should be adequate of the triple therapy will be necessary. For extensive metabolizers, the dual therapy with an increase in the omeprazole dose, or increase in intragastric pH by other methods is recommended. Sometimes, the triple therapy should be applied, but care should be taken for resistance against clarithromycin.

Collectively, poor metabolizers, classified by their *CYP2C19* genotypes, showed the higher effectiveness in anti-*H. pylori* therapy, due to the higher plasma concentration of omeprazole and the higher intragastric pH, and possibly the higher stability of antimicrobials in the higher intragastric pH.

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