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Disposition Kinetics and Metabolism of Omeprazole in Extensive and Poor Metabolizers of S-Mephenytoin 4′-Hydroxylation Recruited from an Oriental Population[1]

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ABSTRACT

To explore the relationship between omeprazole disposition and genetically determined *S*-mephenytoin 4′-hydroxylation phenotype status, we examined the kinetic variables of omeprazole and its two primary metabolites in plasma (5-hydroxyomeprazole and omeprazole sulfone) and the excretion profile of its principal metabolite in urine (5-hydroxyomeprazole) in eight extensive (EMs) and eight poor metabolizers (PMs) recruited from a Korean population. Each subject received a p.o. dose of 20 mg of omeprazole as an enteric-coated formulation, and blood and urine samples were collected up to 24 hr postdose. Omeprazole and its metabolites were measured by high-performance liquid chromatography with ultraviolet detection. The mean omeprazole area under the concentration-time curve (AUC), elimination half-life ($T_{½}$) and apparent p.o. clearance were significantly ($P < .001$) greater, longer and lower, respectively, in PMs than in EMs. The mean peak concentration and AUC of 5-hydroxyomeprazole and AUC ratio of 5-hydroxyomeprazole to omeprazole were significantly ($P < .01$ to $.001$) less in PMs than in EMs. The mean peak plasma concentration, AUC of omeprazole sulfone and ratio of omeprazole sulfone to omeprazole were greater ($P < .001$) and $T_{½}$ was longer ($P < .001$) in PMs than in EMs. The mean cumulative urinary excretion of 5-hydroxyomeprazole up to 24 hr postdose was significantly ($P < .001$) less in PMs than in EMs. In addition, the $\log_{10}$ 4′-hydroxymephenytoin excreted in urine correlated significantly ($P < .01$) with the apparent p.o. clearance of omeprazole and half-lives of omeprazole, 5-hydroxyomeprazole and omeprazole sulfone. The results indicate that the 5-hydroxylation pathway of omeprazole is impaired and the sulfone in plasma is cumulated in PMs of *S*-mephenytoin 4′-hydroxylation. Thus, the metabolic disposition of omeprazole is under a pharmacogenetic control of *S*-mephenytoin 4′-hydroxylase in Korean subjects.

Interindividual differences in drug responsiveness are well recognized in clinical practice. Among factors influencing such differences, pharmacogenetic factor appears to be of clinical importance (Brøsen, 1990; Eichelbaum and Gross, 1990; Wilkinson *et al.*, 1989). One of the most widely studied genetic polymorphisms of drug oxidation is the metabolism of the antihypertensive agent debrisoquin to its 4′-hydroxymetabolite (Brøsen, 1990; Eichelbaum and Gross, 1990; Mahgoub *et al.*, 1977). The more recently discovered polymorphic 4′-hydroxylation of *S*-mephenytoin [mediated *via* P450IIC$_{MP}$ (Wilkinson *et al.*, 1989)], which is independent of debrisoquin-type hydroxylation (Küpfer and Preisig, 1984; Wedlund *et al.*, 1984), is inherited as an autosomal recessive trait (Inaba *et al.*, 1986; Ward *et al.*, 1987). The frequency distribution of metabolic capacity to convert *S*-mephenytoin to 4′-hydroxymephenytoin shows a clear-cut bimodality and is expressed by the two distinct phenotypes: PMs and EMs (Horai *et al.*, 1989; Nakamura *et al.*, 1985; Wedlund *et al.*, 1984; Wilkinson *et al.*, 1989). However, like the debrisoquin-type oxidation pharmacogenetics (Eichelbaum and Gross, 1990), the 4′-hydroxylation polymorphism of *S*-mephenytoin demonstrates a marked interethnic difference in the incidence of the PM phenotype. The frequency of occurrence of the PM phenotype of *S*-mephenytoin is much greater (17–23%) in Oriental populations (Horai *et al.*, 1989; Jurima *et al.*, 1985; Nakamura *et al.*, 1985) compared with that (3–6%) of Caucasian populations (Alván *et al.*, 1990; Jacqz *et al.*, 1988; Wedlund *et al.*, 1984). This genetic polymorphism is relevant to the oxidative metabolism of several clinically important drugs such as propranolol (Ward *et al.*, 1989),

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ABBREVIATIONS: PM, poor metabolizer; EM, extensive metabolizer; ATPase, adenosine triphosphatase; HPLC-UVD, high-performance liquid chromatography with ultraviolet detection; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; k, slope of the log-linear terminal concentration-time phase; AUC, area under the plasma concentration-time curve; CL_o, apparent p.o. clearance; AUC_m/AUC_p, AUC ratio of metabolite to parent drug.

imipramine (Skjelbo *et al.*, 1991), hexobarbital (Knodell *et al.*, 1988; Yasumori *et al.*, 1990), mephobarbital (Jacqz *et al.*, 1986), proguanil (Helsby *et al.*, 1990; Ward *et al.*, 1991) and diazepam (Bertilsson *et al.*, 1989; Sohn *et al.*, 1992).

Omeprazole, a substituted benzimidazole, is a selective inhibitor of H^+/K^+-ATPase proton pump in gastric parietal cells (Fellenius *et al.*, 1982; Wallmark *et al.*, 1983). Its therapeutic potential has been documented as a potent long-acting inhibitor of gastric acid secretion for use in the treatment of duodenal ulcer, refractory gastroesophageal reflux disease, Zollinger-Ellison syndrome and other related hypersecretory conditions (Holt and Howden, 1991; Maton, 1991; McTavish *et al.*, 1991). Omeprazole is metabolized extensively by the liver (Clissold and Campoli-Richards, 1986; Howden, 1991) and its main metabolites are omeprazole sulfone, 5-hydroxyomeprazole and omeprazole sulfide (Clissold and Campoli-Richards, 1986; Regårdh, 1986; Regårdh *et al.*, 1990; Renberg *et al.*, 1989). The pharmacokinetic profile of omeprazole has been well characterized in humans (Clissold and Campoli-Richards, 1986; Howden *et al.*, 1984; McTavish *et al.*, 1991; Regårdh, 1986), indicating that omeprazole is absorbed rapidly and completely from the gastrointestinal tract when given in a sodium bicarbonate buffer to avoid gastric acid degradation. However, omeprazole concentrations in plasma show a pronounced interindividual variability with administering the same doses (Andersson *et al.*, 1990a; Howden, 1991; Howden *et al.*, 1984; Regårdh *et al.*, 1990). Because omeprazole is metabolized extensively by the hepatic cytochrome P450 system (Diaz *et al.*, 1990; Jensen and Gugler, 1986) and exhibits wide interindividual variability in plasma concentration, a question is arisen as to whether any genetically determined factor(s) would be related to its metabolic disposition. Indeed, *S*-mephenytoin 4′-hydroxylase has been suggested to be responsible for the metabolism of omeprazole. However, this suggestion has come mainly from the indirect findings: the slow metabolizers of omeprazole are also slow metabolizers of diazepam (Andersson *et al.*, 1990b), whose metabolism is apparently related to the genetically determined *S*-mephenytoin polymorphism (Bertilsson *et al.*, 1989; Sohn *et al.*, 1992). Although only studied in a limited number of subjects, it has been reported that slow omeprazole metabolizers are also poor *S*-mephenytoin 4′-hydroxylators (Andersson *et al.*, 1990c), but no direct evidence has been presented for the relationship between *S*-mephenytoin's pharmacogenetic polymorphism and omeprazole's metabolic disposition or the pharmacokinetics of its metabolites.

The present study, therefore, was undertaken to investigate the pharmacokinetic disposition and metabolism of omeprazole in EMs and PMs of genetically determined *S*-mephenytoin 4′-hydroxylation polymorphism in an Oriental (Korean) population where the incidence of PMs has been found to be 13% (Sohn *et al.*, 1992). We also investigated the pharmacokinetic profiles of the two principal metabolites of omeprazole, 5-hydroxyomeprazole and omeprazole sulfone, in relation to the *S*-mephenytoin 4′-hydroxylation phenotype status.

Methods

Subjects. Sixteen male, unrelated, healthy Korean subjects were recruited from a population study on *S*-mephenytoin 4′-hydroxylation polymorphism and participated in the current panel study. They had previously been phenotyped for the individual ability to 4′-hydroxylate mephenytoin using the amount of 4′-hydroxymephenytoin excreted in the 8-hr urine after taking a p.o. dose of 100 mg of racemic mephenytoin. Their individual capacities for *S*-mephenytoin 4′-hydroxylation and phenotype status are shown in figure 1. Eight of the subjects were EMs (age, 21–41 yr; weight, 55–67 kg; height, 168–178 cm), whereas the remaining eight were determined to be PMs (age, 21–31 yr; weight, 60–72 kg; height, 168–180 cm). Their demographic data and 4′-hydroxylation capacity variables of *S*-mephenytoin are listed in table 1. They were members of laboratory personnel or medical school students, and were informed both verbally and in writing about the experimental procedure and the purpose of the study. Each subject gave his written consent before the study, the protocol of which was approved by the Ethics Committees of the Gyeongsang National University Hospital (Chinju, Korea) and of the Seoul National University Hospital (Seoul, Korea). Each subject was physically normal and had no antecedent history of significant medical illness or hypersensitivity to any drugs. The subjects received a physical examination with screening blood chemistries, a complete blood count and urinalysis before being admitted to the study. They were asked to refrain from any medications, including alcohol and over-the-counter drugs, for at least 1 week before and throughout the study period.

Study protocol. The participants came to the study site after an overnight fast. Each of them received a p.o. dose of 20 mg of omeprazole as the enteric-coated formulation (Losec, Yuhan Co., Seoul, Korea) with 200 ml of water. A lunch was served 3 hr after the drug ingestion. Each subject took the same volume of water to replace fluid loss as the volume of urine voided after the drug ingestion. Venous blood samples (10 ml each) were collected into heparinized tubes from an antecubital vein using an in-dwelling butterfly cannula, which was kept patent with a heparin lock, immediately before the drug administration and at 0.5, 1, 1.5, 2, 3 and 4 hr postdose. Subsequent blood samples at 6, 8, 10, 12 and 24 hr were drawn by separate venipuncture into heparinized vacutainer tubes. The samples were spun immediately after the collection, and the plasma samples were stored at −80°C until assayed.

Timed urine collections were made at a 2-hr interval for the first 4 hr followed by the collections at 8, 12 and 24 hr. Immediately after collecting each of urine samples, the volume was measured and the pH was adjusted to 7 to 8 with 1 M Na_2CO_3. Aliquots (10 ml) were stored frozen at −80°C until analyzed.

All of the plasma and urine samples from Korea were packed in dry ice and flown to Tokyo and remained frozen on arrival at the National Medical Center in Tokyo where they were assayed.

Assay of omeprazole and its two metabolites. The concentrations of omeprazole and its two primary metabolites, 5-hydroxyomeprazole and omeprazole sulfone, in plasma and its principal metabolite, 5-hydroxyomeprazole, in urine samples were determined by a HPLC-UVD according to a method developed recently by our group (Kobayashi *et al.*, 1992). In brief, the assay consisted of the following procedures: after adding 100 μl of phenacetin (as an internal standard) solution (0.2 mg/ml in methanol), 0.25 g of sodium chloride and 500 μl of 0.5 M phosphate buffer (pH 8.0) to 1 ml of the samples, extraction was conducted by shaking with 5 ml of dichloromethane. After centrifuging, the organic layer was transferred to a glass tube and evaporated by vacuum evaporator at 40°C. The residue was then reconstituted with 200 and 300 μl of the mobile phase in urine and plasma, respectively. For plasma, the reconstituted residue was passed through a 0.45-μm filter (Gelman Sciences Ltd., Ann Arbor, MI), and 30 μl of the filtrate was injected into the HPLC apparatus. For urine, 10 or 30 μl of the reconstituted residue was injected directly into the HPLC apparatus. The HPLC system consisted of a model L-6000 pump, a model L-4000 UV absorbance detector set at a wavelength of 302 nm, a model AS-2000 autosampler, a model D-2500 integrator (Hitachi Ltd., Tokyo, Japan) and a 4.6 mm × 25 cm CAPCELL PAK C_{18} SG 120 column (Shiseido Co. Ltd., Tokyo, Japan). The mobile phase consisted of 0.05 M phosphate buffer (pH 8.5)-acetonitrile (75:25, v/v), at a flow rate of 1.0 ml/min. Under these HPLC-UVD conditions the retention times were 5.8 min for 5-hydroxyomeprazole, 9.5 min for omeprazole sulfone, 12.9 min for phenacetin and 15.8 min for omeprazole. The lower detection limits, defined as the lowest concentration for which the signal-to-noise ratio was at least 5, were ≅ 3 ng/ml for

omeprazole and its metabolite(s) in plasma and urine. Recoveries of the analytes and internal standard were > 93%. The intra- and inter-assay coefficients of variation were < 9.1 and 6.4% for plasma samples and < 2.9 and 3.9% for urine samples, respectively.

Pharmacokinetic data analysis. The C_{max}s and the t_{max}s of omeprazole and its two metabolites, 5-hydroxyomeprazole and omeprazole sulfone, were determined from the observed concentration-time data. The ks of the analytes were calculated by the linear least-squares regression analysis of the respective log-linear plasma concentration-time data. The $T_{1/2}$s of omeprazole and its two metabolites were calculated as:

$$T_{1/2} = 0.693/k$$

The AUC from zero hr to the last measurable sampling time (AUC_0^t) of each of the three analytes was calculated by the trapezoidal rule. The AUC from zero hr to infinity (AUC_0^∞) was calculated as:

$$AUC_0^\infty = AUC_0^t + C_t/k$$

where C_t represents the last measurable or detectable plasma concentrations with the assay in both the EM and PM groups. The CL_o of omeprazole was calculated as:

$$CL_o = \text{dose}/AUC_0^\infty$$

The percentage cumulative molar amount of 5-hydroxyomeprazole relative to the administered dose of omeprazole excreted in urine up to 24 hr postdose was plotted against the time.

Statistical analysis. The data are expressed as mean ± S.E. throughout the text. Differences in pharmacokinetic data between the EM and PM groups were evaluated statistically using the Student's t test, and Spearman's rank correlations (r_s) were assessed where appropriate. A P value of < .05 was considered statistically significant.

Results

No clinically undesirable signs and symptoms possibly attributed to the administration of omeprazole were recognizable throughout the study period. All subjects completed the study according to the protocol. As listed in table 1, EMs recruited from the population study (fig. 1) had a mean urinary 4′-hydroxymephenytoin excretion of 20.81 ± 2.72% (range, 11.59–36.76%), which is approximately 60-fold greater compared with that of PMs (0.32 ± 0.04%; range, 0.13–0.53%). The $\log_{10}$% urinary excretion of 4′-hydroxymephenytoin ranged from 1.06 to 1.57 among eight EMs, whereas it ranged from −0.89 to −0.28 among eight PMs. The mean hydroxylation index, calculated as the dose of S-mephenytoin (*i.e.*, 50% of the 100 mg of racemic mephenytoin) divided by the molar amount of 4′-hydroxymephenytoin excreted in the postdose 8-hr urine, was about 65-fold greater in PMs than in EMs. Thus, the data on the disposition and metabolism of omeprazole as described below should be viewed in the light of the difference in the genetically determined S-mephenytoin 4′-hydroxylation status between the two phenotype groups.

TABLE 1

Subject characteristics and mephenytoin 4′-hydroxylation capacity variables in EMs and PMs of S-mephenytoin

The data are expressed as mean ± S.E.

	EMs (n = 8)	PMs (n = 8)
Age (yr)	25.1 ± 2.2	23.9 ± 1.4
Weight (kg)	60.4 ± 1.3	65.5 ± 1.2
Height (cm)	171.3 ± 1.2	172.5 ± 1.2
4′-Hydroxymephenytoin[a]	20.81 ± 2.72	0.32 ± 0.04
$\log_{10}$ 4′-hydroxymephenytoin	1.32 ± 0.05	−0.49 ± 0.06
Hydroxylation index[b]	2.7 ± 0.3	182.5 ± 29.2
$\log_{10}$ hydroxylation index	0.43 ± 0.05	2.26 ± 0.06

[a] Urinary excretion percentage of the dose of mephenytoin administered (100-mg racemic dose).

[b] The dose of S-mephenytoin (*i.e.*, 50% of the 100-mg racemic dose) divided by the molar amount of 4′-hydroxymephenytoin excreted in urine over 8 hr.

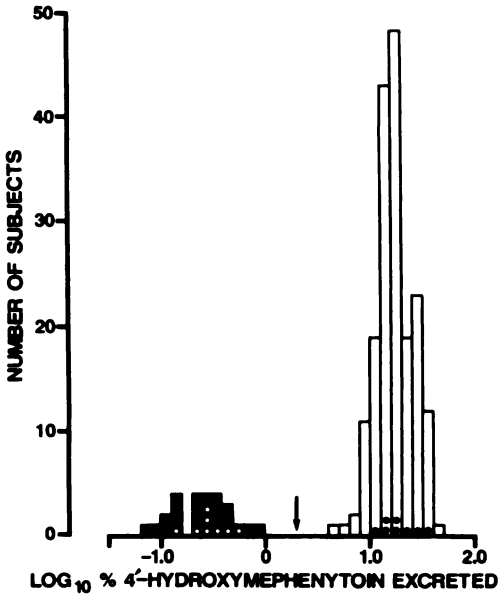

Fig. 1. Frequency distribution histogram of the $\log_{10}$ 8-hr urinary excretion of 4′-hydroxymephenytoin (as percentage of the dose administered) in 206 Korean subjects, and the individual phenotyping status of the subjects participated in the current panel study. Open and shaded areas in the histogram indicate EMs and PMs of S-mephenytoin 4′-hydroxylation. Arrow, a visual antimode at 0.3 to discriminate between the EM and PM groups. The symbols (⊡ = EMs; ■ = PMs) in bars represent the participants of the panel study who were recruited from the population.

Concentration-time profiles of omeprazole and its principal metabolites in plasma. The mean (±S.E.) plasma concentration-time curves of omeprazole and its primary metabolites, 5-hydroxyomeprazole and omeprazole sulfone, in EMs and PMs who took an p.o. dose of 20 mg of omeprazole are shown in figure 2, A, B and C, respectively. The mean plasma omeprazole concentrations were significantly (P < .01 to .001) greater at all time points after the postdose 1 hr in PMs than in EMs (fig. 2A). The mean plasma concentration of omeprazole was 91.1 ± 14.3 (range, 46.1 to 181.8) ng/ml at 12 hr postdose in PMs, whereas it became lower than the detection limit of the assay in all of EMs; omeprazole was still detectable at 24 hr postdose in all of PMs.

The mean plasma concentration-time curves of 5-hydroxyomeprazole (fig. 2B) and omeprazole sulfone (fig. 2C) also demonstrated marked interphenotypic differences. The mean plasma 5-hydroxyomeprazole concentrations at 0.5 to 4 hr postdose were significantly (P < .05 to .001) lower in PMs than in EMs. Thereafter, the mean plasma concentrations up to 10 hr postdose revealed no statistical differences between the two groups. 5-Hydroxyomeprazole in plasma became unmeasurable with the assay at more than 10 and 12 hr postdose in EMs and PMs, respectively. 5-Hydroxyomeprazole in plasma was undetectable throughout the total sampling time period in one PM subject whose amount of 4′-hydroxymephenytoin excreted in the 8-hr urine and hydroxylation index were 0.46% and 108.11, respectively. The mean kinetic data on 5-hydroxyomeprazole (table 2) were, therefore, estimated from the data from the remaining seven PMs.

The concentration-time profile of omeprazole sulfone (fig.

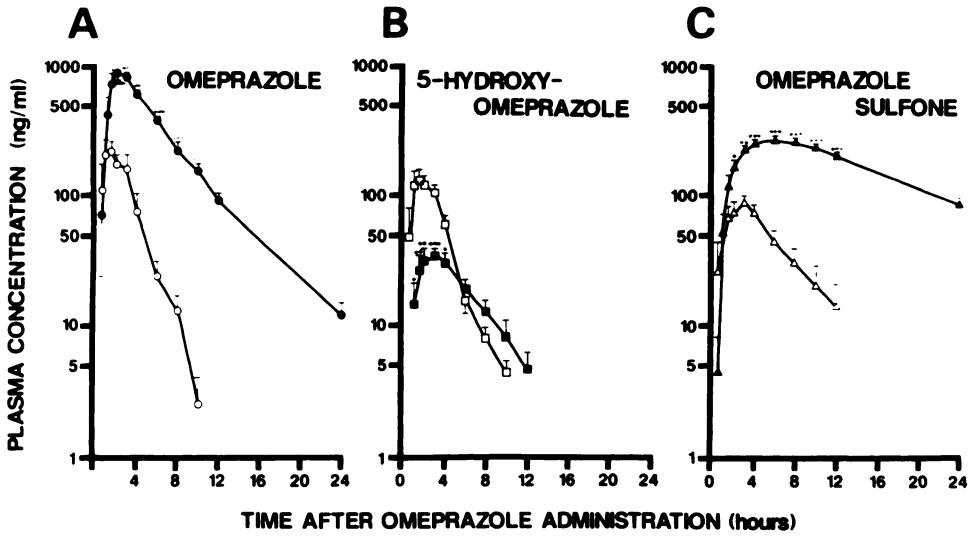

Fig. 2. Plasma concentration-time profiles of omeprazole (A), 5-hydroxyomeprazole (B) and omeprazole sulfone (C) after a p.o. 20-mg dose of omeprazole administered to eight EMs (open symbols) and eight PMs (closed symbols) of *S*-mephenytoin. The data shown in B (■) were derived from seven PMs because plasma levels were lower than the detection limit of the assay (*i.e.*, < 3 ng/ml) throughout the sampling period in one PM subject. The data are given as mean ± S.E. *P < .05, **P < .01 and ***P < .001 compared with EMs.

TABLE 2

Pharmacokinetic data of omeprazole and its two principal metabolites in EMs and PMs of *S*-mephenytoin

The data are given as mean ± S.E. AUC_m, area under the plasma concentration-time curve of the metabolite from 0 hr to infinity; AUC_p, area under the plasma concentration-time curve of the parent drug (*i.e.*, omeprazole) from 0 hr to infinity.

	Omeprazole		5-Hydroxyomeprazole		Omeprazole Sulfone	
	EMs	PMs	EMs	PMs	EMs	PMs
C_{max} (ng/ml)	381.1 ± 54.4	1049.9 ± 72.4***	209.6 ± 18.2	46.2 ± 4.6[a]***	102.5 ± 13.5	280.2 ± 12.0***
t_{max} (hr)	1.7 ± 0.3	2.3 ± 0.2	1.7 ± 0.3	2.3 ± 0.2	2.0 ± 0.4	6.3 ± 0.7***
$T_{½}$ (hr)	1.4 ± 0.2	3.2 ± 0.2***	1.5 ± 0.2	3.4 ± 0.4**	2.5 ± 0.4	10.6 ± 0.9***
AUC_0^t (ng/ml·hr)[b]	749.5 ± 82.4	4482.0 ± 264.0***	491.1 ± 29.4	231.0 ± 27.3***	541.8 ± 91.8	2507.7 ± 139.4***
AUC_0^∞ (ng/ml·hr)	778.5 ± 78.7	5330.5 ± 392.4***	508.3 ± 28.7	292.1 ± 40.0**	685.9 ± 176.2	5699.1 ± 353.8***
CL_o (ml/hr/kg)	475.9 ± 64.2	59.5 ± 3.6***				
AUC_m/AUC_p			0.71 ± 0.08	0.05 ± 0.01***	0.80 ± 0.12	1.08 ± 0.05***

[a] The mean ± S.E. data were obtained from the seven PM subjects because plasma concentrations of 5-hydroxyomeprazole in one of them were under the detection limit of the assay throughout the sampling period.

[b] AUC_0^{10} for omeprazole and 5-hydroxyomeprazole, and AUC_0^{12} for omeprazole sulfone.

** P < .01 as compared with EMs; *** P < .001 as compared with EMs.

2C) had a trend similar to that of the parent drug (fig. 2A): there were statistically significant (P < .05 to .001) differences in the mean plasma omeprazole sulfone concentrations between the two groups from the postdose 2 to 12 hr. Furthermore, the plasma concentrations of omeprazole sulfone, like omeprazole (fig. 2A), could be followed up to 24 hr postdose in all of PMs (46.3–126.8 ng/ml), whereas in all plasma samples from EMs these concentrations were below the quantitation limit of the assay.

Pharmacokinetic analysis of omeprazole and its metabolites in plasma. Individual data on the major pharmacokinetic variables of omeprazole and its two metabolites in the two groups are shown in figure 3, A-D, indicating marked interphenotypic differences in the kinetic variables of the respective analytes. However, the elimination $T_{½}$ values for 5-hydroxyomeprazole in three PM subjects overlapped the range observed in EMs (fig. 3C).

The mean kinetic data are summarized in table 2. There were highly significant (P < .001) interphenotypic differences between the two groups in the mean kinetic parameters of omeprazole except for the t_{max} (table 2): the mean AUC and CL_o values were approximately 6 to 7 times greater and smaller, respectively, in PMs than in EMs. The mean kinetic values for omeprazole sulfone showed similar differences between the two groups as observed with omeprazole: the mean C_{max} and AUC values were significantly (P < .001) greater in PMs than in

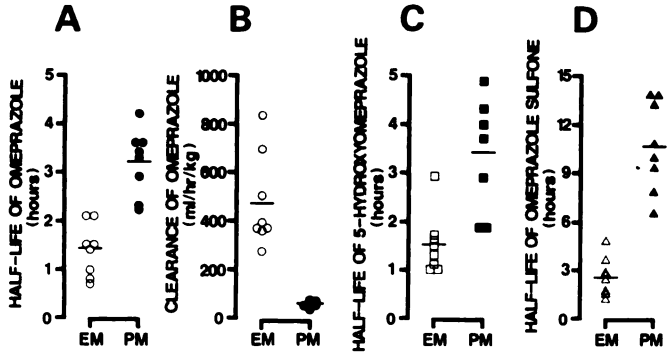

Fig. 3. Individual data on plasma $T_{½}$ (A) and CL_o (B) of omeprazole, and plasma $T_{½}$ of 5-hydroxyomeprazole (C) and omeprazole sulfone (D) in EMs (open symbols) and PMs (closed symbols) of *S*-mephenytoin. The horizontal bars indicate the respective mean values. The data plotted in C (■) were obtained from seven PMs because plasma levels of 5-hydroxyomeprazole in one PM subject were undetectable with the assay (*i.e.*, < 3 ng/ml) throughout the sampling period.

EMs. The mean $T_{½}$ and AUC_m/AUC_p also differed significantly (P < .001) between the two groups.

In contrast, the kinetic data on 5-hydroxyomeprazole showed a behavior opposite to those on omeprazole and omeprazole sulfone (table 2): the mean C_{max}, AUC and AUC_m/AUC_p were significantly (P < .01 to .001) less in PMs than in EMs,

implying that the hydroxylation of omeprazole to 5-hydroxyomeprazole is considerably impaired in PMs.

Correlations among kinetic variables of omeprazole and its metabolites. Relationships were assessed in the elimination $T_{1/2}$ and AUC values of the three analytes among each other, and significant correlations were observed as follows: for $T_{1/2}$, omeprazole *vs.* 5-hydroxyomeprazole ($r_s = 0.841$, $P < .01$), omeprazole *vs.* omeprazole sulfone ($r_s = 0.764$, $P < .01$) and 5-hydroxyomeprazole *vs.* omeprazole sulfone ($r_s = 0.640$, $P < .01$); for AUC_0^{10} or AUC_0^{12}, omeprazole *vs.* 5-hydroxyomeprazole ($r_s = -0.736$, $P < .01$), omeprazole *vs.* omeprazole sulfone ($r_s = 0.856$, $P < .01$) and 5-hydroxyomeprazole *vs.* omeprazole sulfone ($r_s = -0.693$, $P < .01$); and for AUC_0^∞, omeprazole *vs.* 5-hydroxyomeprazole ($r_s = -0.529$, $P < .01$), omeprazole *vs.* omeprazole sulfone ($r_s = 0.968$, $P < .01$) and 5-hydroxyomeprazole *vs.* omeprazole sulfone ($r_s = -0.507$, $P < .01$).

Relationships of kinetic variables of omeprazole and its metabolites *versus* S-mephenytoin 4′-hydroxylation capacity. Significant correlations existed between the $\log_{10}$ urinary excretion of 4′-hydroxymephenytoin and the elimination $T_{1/2}$ of omeprazole (fig. 4A), and the CL_o (fig. 4B) in the subjects studied ($r_s = -0.720$ and 0.793, respectively, $P < .01$). Similarly, significant correlations existed between the capacity of 4′-hydroxylation of *S*-mephenytoin and the $T_{1/2}$ of 5-hydroxyomeprazole (fig. 4C) and of omeprazole sulfone (fig. 4D): there were strong negative correlations between these evaluated variables ($r_s = -0.877$ and -0.714, respectively, $P < .01$). In addition, when relationships were evaluated between the $\log_{10}$ urinary excretion of 4′-hydroxymephenytoin *vs.* C_{max} and AUC_0^∞ values for the three analytes, *vs.* AUC_0^{10} for omeprazole and 5-hydroxyomeprazole, *vs.* AUC_0^{12} for omeprazole sulfone, and *vs.* AUC_m/AUC_p for 5-hydroxyomeprazole and omeprazole sulfone, all of these correlations were statistically significant ($r_s \geq +$ or $-$ 0.636, $P < .01$).

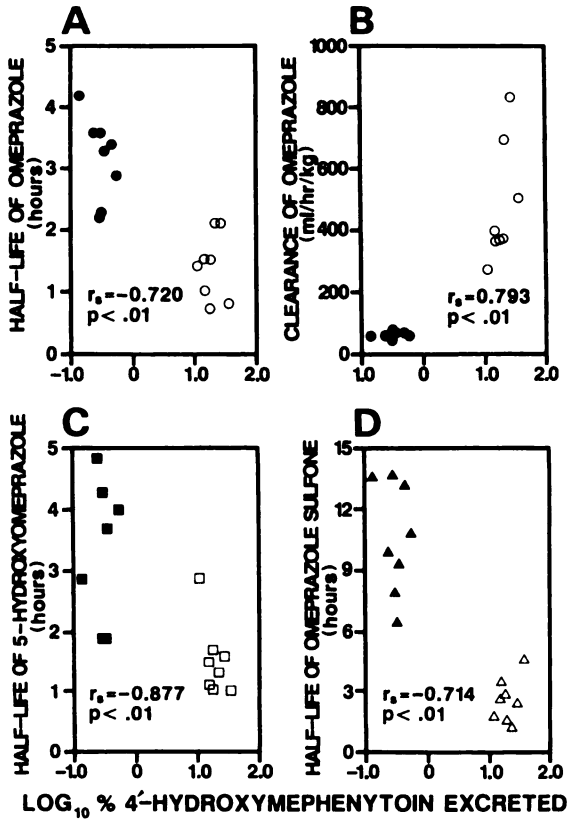

Fig. 4. Correlations between $\log_{10}$ 8-hr urinary excretion of 4′-hydroxymephenytoin and plasma $T_{1/2}$ (A) or CL_o (B) of omeprazole, and plasma $T_{1/2}$ of 5-hydroxyomeprazole (C) and omeprazole sulfone (D) (open symbols = EMs and closed symbols = PMs of *S*-mephenytoin). Correlation coefficients (r_s) were assessed using Spearman's rank correlation test. The r_s value in C came from $n = 15$ because plasma levels of 5-hydroxyomeprazole in one PM subject were undetectable with the assay (*i.e.*, < 3 ng/ml) throughout the sampling period.

Urinary excretion of 5-hydroxyomeprazole. The time course of postdose 24-hr cumulative urinary excretion of 5-hydroxyomeprazole observed in the two groups is shown in figure 5. The amount excreted rose rapidly within the first 8 hr and then flattened out during the 12- to 24-hr period in the EM group. In the PM group it rose gradually during the up to 12 hr and flattened out during the 12- to 24-hr period as observed in the EM group. At the first 2 hr after the p.o. dosing of omeprazole, the mean excretion of 5-hydroxyomeprazole was only 0.84 ± 0.21% in the PM group compared with the mean of 5.97 ± 0.94% in the EM group (*i.e.*, a 7-fold difference). This interphenotypic difference was observed throughout the urine collection period: at all timed collection periods the mean urinary excretion amounts were significantly ($P < .01$ to .001) less in PMs than in EMs (fig. 5). The mean cumulative excretion at 24 hr was 13.51 ± 0.90% in EMs and 5.62 ± 0.74% in PMs, and thus the interphenotypic difference became smaller at longer collection times. Both omeprazole and omeprazole sulfone were unmeasurable in urine samples of any of the subjects collected during the study period.

Discussion

Genetically determined *S*-mephenytoin polymorphism is now known to affect the oxidative metabolism of several clinically important drugs (Wilkinson *et al.*, 1989). However, its clinical significance, to our knowledge, appears to remain unclear at present. We have reported recently that the two native Oriental (Japanese and Chinese) populations had a greater frequency (17–23%) of the PM phenotype for *S*-mephenytoin 4′-hydroxylation (Horai *et al.*, 1989) compared with that (3–6%) reported from Caucasian populations (Alván *et al.*, 1990; Jacqz *et al.*, 1988; Küpfer and Preisig, 1984; Wedlund *et al.*, 1984). The Korean population from which the 16 subjects were recruited for the panel study exhibited a frequency of 13% of the PM

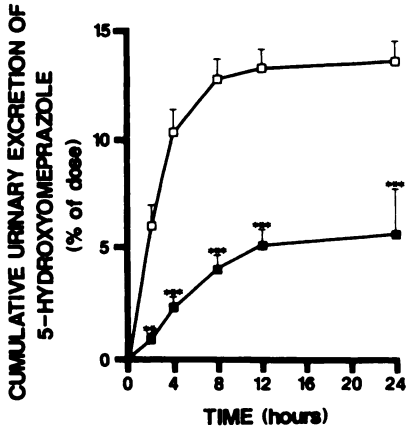

Fig. 5. Cumulative urinary excretion-time data of 5-hydroxyomeprazole after a p.o. dose of 20 mg of omeprazole administered to eight EMs (□) and eight PMs (■) of *S*-mephenytoin. The data are given as mean ± S.E. **P < .01 and ***P < .001 compared with EMs.

phenotype (Sohn *et al.*, 1992). Thus, if this pharmacogenetic determinant could have clinical implication, a drug whose metabolism is mediated *via* *S*-mephenytoin 4′-hydroxylase might be of more clinical concern among Oriental patients than among Caucasian patients. A recent short communication by Andersson *et al.* (1990c) reporting that slow omeprazole metabolizers were also poor *S*-mephenytoin 4′-hydroxylators, therefore, prompted us to conduct a more detailed pharmacokinetic study on omeprazole and its two principal metabolites, 5-hydroxyomeprazole and omeprazole sulfone, in EMs and PMs of *S*-mephenytoin who were recruited from an Oriental (Korean) population including a frequency of 13% of the PM phenotype.

The current panel study was conducted only in male subjects. This selection was based upon the following reasons: first, only 4 of the 50 females included in the population ($n = 206$, fig. 1) were 20- to 23-year-old PMs and had a regular menstrual cycle. Second, changes in sex hormones (*i.e.*, progesterone and estrogen) during the menstrual cycle may affect the hepatic microsomal enzyme system (Kato, 1974; Tephly and Mannering, 1968). Third, gender differences in the pharmacokinetics of several drugs have been well documented (Greenblatt *et al.*, 1980; Kato, 1974; Wilson, 1984). Thus, selecting only the male subjects for the panel study on the disposition and metabolism of omeprazole was considered appropriate in terms of eliminating one of the potentially confounding factors influencing drug metabolism and disposition, although whether the metabolic disposition of omeprazole would be affected by gender factor is totally unknown. With this limitation of the selection of our study subjects, our results indicate that 1) the metabolic pathways of omeprazole in PMs are characterized by an impaired 5-hydroxylation; 2) the further metabolism of 5-hydroxyomeprazole and omeprazole sulfone to the respective yet uncharacterized metabolites may also be impaired in PMs; and 3) the metabolic disposition of omeprazole is under a pharmacogenetic control of *S*-mephenytoin 4′-hydroxylase in the Korean subjects.

Our observation that both omeprazole and omeprazole sulfone were unmeasurable in urine samples of any of the subjects collected during the study period is in agreements with the previous observations that the parent drug and its sulfone metabolite were undetectable in the human urine with an HPLC assay after administering [^{14}C]omeprazole to healthy persons (Regårdh *et al.*, 1990) and patients (Naesdal *et al.*, 1986) or nonlabeled omeprazole to healthy persons (Prichard *et al.*, 1985). Thus, the interphenotypic differences in the kinetic data of these two compounds are not due to those in the elimination route *via* kidneys.

The pharmacokinetic data observed in our EM group are consistent with the observation that most individuals exhibit rapid metabolism of omeprazole with an elimination $T_{1/2}$ ranging from 0.5 to 1 hr but that a few individuals have a much slower metabolism of omeprazole such that their $T_{1/2}$ and AUC values were about 3 times longer and 10 times greater, respectively (Andersson *et al.*, 1990a). Because omeprazole is metabolized completely and its urinary recovery as the unchanged form is negligible (Clissold and Campoli-Richards, 1986; Howden, 1991; Maton, 1991; Regårdh *et al.*, 1990), significant differences in the mean kinetic variables (table 2) are explainable by the interphenotypic differences in *S*-mephenytoin metabolic capacities. The mean CL_o was about 8 times lower and the mean AUC terms were about 6 to 7 times greater in the PM than in the EM group. Furthermore, the strong positive correlation between the metabolic capacity of *S*-mephenytoin (*i.e.*, $\log_{10}$% urinary excretion of 4′-hydroxymephenytoin) and CL_o of omeprazole (fig. 4B) provides a strong evidence that the metabolism of omeprazole and S-mephenytoin is under a similar genetic or coregulatory control.

One of the primary metabolites, 5-hydroxyomeprazole, appeared in plasma more slowly and showed a longer apparent $T_{1/2}$ in the PM than in the EM group (fig. 2B; table 2). The mean AUC ratio of 5-hydroxyomeprazole to omeprazole (AUC_m/AUC_p) and cumulative urinary excretion-time data of 5-hydroxyomeprazole at all urine collection periods were significantly lower in PMs than in EMs (table 2; fig. 5, respectively). In addition, there was a close correlation between the $T_{1/2}$ and AUC_m/AUC_p values and the $\log_{10}$% urinary excretion of 4′-hydroxymephenytoin (for $T_{1/2}$, $r_s = -0.877$; for AUC_m/AUC_p, $r_s = 0.845$, $P < .01$). Taken together, these findings indicate that 5-hydroxyomeprazole is formed from omeprazole *via* *S*-mephenytoin 4′-hydroxylase and may also be metabolized further to yet unknown metabolite(s) *via* the same isozyme. However, we observed that the respective mean $T_{1/2}$ values for 5-hydroxyomeprazole were fairly close to those for omeprazole in the EM and PM groups, suggesting that the rate limiting step of the elimination of 5-hydroxyomeprazole would be the formation of the metabolite from omeprazole. Thus, the correlations between $\log_{10}$ urinary excretion of 4′-hydroxymephenytoin and the kinetic variables of 5-hydroxyomeprazole appear to be a simple reflection of their dependence on the formation rate of 5-hydroxyomeprazole but not on the elimination rate of the metabolite. Thus, 5-hydroxyomeprazole is formed *via* $P450IIC_{MP}$, but the further metabolism of 5-hydroxyomeprazole appears to be not.

The plasma concentration-time profile and kinetic variables of omeprazole sulfone showed a behavior similar to those of the parent drug (fig. 2; table 2, respectively): omeprazole sulfone was eliminated from plasma at a much lower rate in the PM than in the EM group (fig. 2C). This resulted in the interphenotypic differences in several kinetic variables: the mean apparent elimination $T_{1/2}$ and AUC values were about 5 times longer and 11 times greater, respectively, in the PM than in the EM group (table 2). In addition, a strong correlation ($r_s = 0.764$, $P < .01$) was observed between the elimination $T_{1/2}$ values for omeprazole and its sulfone. The AUCs of omeprazole and omeprazole sulfone also showed a strong correlation ($r_s = 0.968$ for AUC_0^∞ and 0.856 for AUC_0^t, $P < .01$). These findings suggest that the further metabolism of omeprazole sulfone also appears to be mediated *via* *S*-mephenytoin 4′-hydroxylase. In agreement with this speculative explanation, Regårdh *et al.* (1990) have suggested that the further metabolism of omeprazole sulfone to a 5-hydroxy metabolite would be mediated by the same enzyme involved in the hydroxylation of the parent drug.

Omeprazole reaches the gastric parietal cells through the bloodstream after gastrointestinal absorption, and in the secretory canaliculus it is exposed to a pH of < 2.0 and becomes protonated (Clissold and Campoli-Richards, 1986; Maton, 1991). Omeprazole itself is inactive (*i.e.*, a prodrug), but under acidic condition it is converted to the active form, a sulfenamide (Lindberg *et al.*, 1986; Lorentzon *et al.*, 1987) that reacts covalently with the SH groups of cysteine residues on the extracellular surface of the H^+/K^+-ATPase and inhibits the activity of enzyme (Maton, 1991). Therefore, in theory, the greater concentration in the systemic circulation, the more amount in

gastric parietal cells available for converting to the active form. In this context, patients with a PM phenotype of *S*-mephenytoin 4′-hydroxylation polymorphism would be expected to have a greater exposure to omeprazole because the AUC was about 6 to 7 times greater compared with EMs (table 2) and, therefore, a greater antisecretory effect and/or a longer duration of action of omeprazole might be present. A study (Lind *et al.*, 1983) has shown that the degree of inhibition of acid secretion by omeprazole is related to the individual AUC in humans. In addition, the steady-state inhibition of acid secretion during treatment with the same daily dose of 20 mg of omeprazole has been reported to vary widely from person to person: ranges of 35 to 65%, based on measuring acid secretion 24 hr after drug administration (Lind *et al.*, 1983 and 1988) and 30 to 100%, based on measuring 24-hr gastric acidity by a continuous intragastric pH monitoring (Naesdal *et al.*, 1987; Sharma *et al.*, 1984) have been demonstrated. In all of these studies the inter-subject variabilities in the pharmacodynamic responsiveness to omeprazole have not been evaluated in relation to the individual *S*-mephenytoin 4′-hydroxylation capacities. Thus, whether and to what extent the pharmacodynamic responsiveness to this proton pump inhibitor would be related to the *S*-mephenytoin 4′-hydroxylation capacity of each patient appears to be an intriguing question.

Omeprazole appears to have a wide therapeutic margin (Clissold and Campoli-Richards, 1986). Regårdh *et al.* (1985) have reported that the bioavailability (or AUC) increased with dosage from 40.3% (10 mg) to 58.2% (40 mg) and 96.9% (90 mg), respectively, and suggested that the increase in bioavailability with increased dosage may be due to partial saturation of enzymes responsible for the hepatic first-pass metabolism. Andersson (1991) has reported that the interphenotypic difference in the bioavailability or AUC of omeprazole becomes smaller during the multiple dosing because of increased omeprazole concentrations due to saturable metabolism in EMs, but not in PMs, of *S*-mephenytoin 4′-hydroxylation. Therefore, it seems unlikely that treatment with therapeutically recommended doses of omeprazole will result in a clinically significant implication for patients with the different phenotypes of *S*-mephenytoin 4′-hydroxylation who receive this proton pump inhibitor in the repetitive doses. Nevertheless, a controversial issue concerning the safety of omeprazole administered in the multiple dosing has been its ability to produce hypergastrinemia and hyperplasia of enterochromaffin-like cells, thereby resulting in gastric carcinoid tumors in rats (Larsson *et al.*, 1988a,b), and the implications of these animal findings for humans (Berlin, 1991; Maton, 1991). Any drugs, like omeprazole, capable of profoundly inhibiting gastric acid secretion stimulate the release of gastrin from antral G cells and lead to an increase in plasma gastrin concentration (Dockray and Gregory, 1989). Indeed, omeprazole (10, 20 or 40 mg/day administered in the morning for 2 weeks) produced a dose-related increase in gastrin concentrations in humans (Karnes *et al.*, 1990). A recent review article (Maton, 1991) has summarized the clinical data on omeprazole-induced, interindividual changes in plasma gastrin concentrations from the predose or base-line values: omeprazole causes a 2- to 4-fold increase and occasionally a 10-fold increase. Coupled with the above-mentioned findings and by accepting the hypothesis, that long-term treatment with omeprazole may produce sufficient hypergastrinemia to cause hyperplasia of enterochromaffin-like cells and possibly carcinoid tumors in some patients (Maton, 1991), whether patients with mephenytoin 4′-hydroxylation deficiency receiving a long-term omeprazole therapy would be more prone to develop a hypergastrinemia-related hyperplasia of enterochromaffin-like cells might appear to be a clinical concern. In our opinion, a conclusive statement that the rat model is a false indicator of risk in humans (Berlin, 1991) seems to be an unwarranted consideration for all patients receiving an omeprazole therapy, because previous clinical studies on omeprazole kinetics and dynamics have not been assessed in relation to genetically determined S-mephenytoin phenotype status.

In closing, the metabolism of omeprazole cosegregates with genetically determined *S*-mephenytoin 4′-hydroxylation capacity that differs interindividually and interethnically. Although the clinical implications of pharmacogenetically related omeprazole's metabolism and disposition remain totally obscure at present, we are tempted to consider the pharmacogenetic determinant as one of the confounding factors influencing the metabolic disposition of omeprazole as well as possibly the interindividual variability in the pharmacodynamic responsiveness to this proton pump inhibitor observed in clinical practice.

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