Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes

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Aims

Omeprazole is mainly metabolized by the polymorphic cytochrome P450 (CYP) 2C19. The inhibitory effect of fluvoxamine, an inhibitor of CYP2C19 as well as CYP1A2, on the metabolism of omeprazole was compared between different genotypes for CYP2C19.

Methods

Eighteen volunteers, of whom six were homozygous extensive metabolizers (EMs), six were heterozygous EMs and six were poor metabolizers (PMs) for CYP2C19, participated in the study. A randomized double-blind, placebo-controlled crossover study was performed. All subjects received two six-day courses of either daily 50 mg fluvoxamine or placebo in a randomized fashion with a single oral 40 mg dose of omeprazole on day six in both cases. Plasma concentrations of omeprazole and its metabolites, 5-hydroxyomeprazole, omeprazole sulphone, and fluvoxamine were monitored up to 8 h after the dosing.

Results

During placebo administration, geometric means of peak concentration (C_{max}), under the plasma concentration-time curve from 0 to 8 h ($AUC(0,8\text{ h})$) and elimination half-life ($t_{1/2}$) of omeprazole were 900 ng ml⁻¹, 1481 ng ml⁻¹ h, and 0.6 h in homozygous EMs, 1648 ng ml⁻¹, 4225 ng ml⁻¹ h, and 1.1 h in heterozygous EMs, and 2991 ng ml⁻¹, 11537 ng ml⁻¹ h, and 2.8 h in PMs, respectively. Fluvoxamine treatment increased C_{max} of omeprazole by 3.7-fold (95%CI, 2.4, 5.0-fold, $P < 0.01$) and 2.0-fold (1.4, 2.6-fold, $P < 0.01$), $AUC(0,8\text{ h})$ by 6.0-fold (3.3, 8.7-fold, $P < 0.001$) and 2.4-fold (1.7, 3.2-fold, $P < 0.01$), $AUC(0,\infty)$ by 6.2-fold (3.0, 9.3-fold, $P < 0.01$) and 2.5-fold (1.6, 3.4-fold, $P < 0.001$) and prolonged $t_{1/2}$ by 2.6-fold (1.9, 3.4-fold, $P < 0.001$) and 1.4-fold (1.02, 1.7-fold, $P < 0.05$), respectively. However, no pharmacokinetic parameters were changed in PMs. The $AUC(0,8\text{ h})$ ratios of 5-hydroxy-omeprazole to omeprazole were decreased with fluvoxamine in homozygous EMs ($P < 0.05$) and heterozygous EMs ($P < 0.01$).

Conclusions

Even a low dose of fluvoxamine increased omeprazole exposure in EMs, but did not increase omeprazole exposure in PMs after a single oral dose of omeprazole. These findings confirm a potent inhibitory effect of fluvoxamine on CYP2C19 activity. The bioavailability of omeprazole might, to some extent, be increased through inhibition of P-glycoprotein during fluvoxamine treatment.

Introduction

Omeprazole is one of the most widely used proton pump inhibitors for the treatment of gastric acid-related disorders [1]. Omeprazole is completely metabolized, mainly by hydroxylation catalyzed by CYP2C19 [2], which shows genetically determined polymorphism, yielding extensive metabolizers (EMs) and poor metabolizers (PMs) [3]. Since the rate of omeprazole hydroxylation correlates with the hydroxylation of S-mephenytoin, the metabolic ratio of 5-hydroxyomeprazole to omeprazole has been used to assess the activity of CYP2C19 [4]. Omeprazole is also metabolized by CYP3A4 to omeprazole sulphone. In PMs, this is the predominant metabolic pathway [5].

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is metabolized in the liver by CYP2D6 and CYP1A2 [6]. Fluvoxamine is regarded as a potent CYP1A2 inhibitor based on many drug interactions of fluvoxamine with caffeine [7], clozapine [8, 9], olanzapine [10], imipramine [11, 12], amitriptyline [13], clomipramine [13, 14] and theophylline [15], each of which is a substrate for CYP1A2. In addition, it has been suggested that fluvoxamine inhibits the metabolism of CYP2C19 substrates such as citalopram [16], omeprazole [17, 18] and chloroguanide hydrochloride (INN, proguanil) [19]. Thus, fluvoxamine has been regarded as a potent inhibitor of not only CYP1A2 but also CYP2C19. Also, fluvoxamine increased plasma concentrations of alprazolam [20], a substrate of CYP3A4 [21], suggesting that fluvoxamine has an inhibitory effect on CYP3A4 to some degree.

Our previous study has shown that low doses of fluvoxamine in EMs for CYP2C19 decreased the area under the plasma concentration-time curve from time 0 to 8 h [AUC(0,8 h)] ratio of 5-hydroxyomeprazole : omeprazole by 3.4-fold [18], suggesting that fluvoxamine has a potent inhibitory effect on CYP2C19 activity. We presumed that no changes in omeprazole concentrations would be found in PMs if this interaction was only due to CYP2C19 inhibition by fluvoxamine. However, there is no published information about the difference in this interaction between EMs and PMs of CYP2C19. Therefore, in the present study, the inhibitory effects of fluvoxamine on the metabolism of omeprazole were compared between three different CYP2C19 genotypes.

Methods

Study design

Eighteen Japanese healthy volunteers (14 males and four females; age range 22–44 years; weight range 40–90 kg) participated in the study after written

informed consent was obtained. The mutated alleles for CYP2C19, *CYP2C19*3*(*3) and *CYP2C19*2*(*2) had been identified using the PCR-RFLP methods of de Morais *et al.* [22], prior to this study. The CYP2C19 genotype analyses revealed five different patterns as follows: *1/*1 in 6, *1/*2 in 3, *1/*3 in 3, *2/*2 in 4 and *2/*3 in 2. These were divided into three groups, homozygous EMs (*1/*1, *n* = 6), heterozygous EMs (*1/*2 and *1/*3, *n* = 6) and PMs (*2/*2 and *2/*3, *n* = 6). The protocol was approved by the Ethics Committee of Hirosaki University School of Medicine.

A randomized double-blind placebo-controlled cross-over study design in two phases was conducted at intervals of 2 weeks. Fluvoxamine (25 mg) as the capsule formulation containing a tablet formulation (Luvox[®], Fujisawa Pharmaceutical Co., Ltd, Osaka, Japan) or matched placebo (as the capsule formulation with the same appearance and size of that of fluvoxamine) was given orally twice a day (09.00 h, 21.00 h) for 6 days. Nine volunteers each as a group were allocated to either of the different drug sequences: placebo-fluvoxamine or fluvoxamine-placebo. On day 6, they took a single oral 40 mg dose of omeprazole (Omepral[®], AstraZeneca Co., Ltd, Osaka, Japan) and 25 mg dose of fluvoxamine or placebo after overnight fasting (09.00 h) with 240 ml of tap water. Compliance of test drugs was confirmed by pill-count. No other medications were taken during the study periods. No meal was allowed until 4 h after the dosing (13.00 h). The use of alcohol, tea, coffee and cola was forbidden during the test days.

Blood sampling

Blood samples (10 ml each) for determination of omeprazole and its metabolites, 5-hydroxyomeprazole and omeprazole sulphone, and fluvoxamine, were taken into heparinized tubes just before and 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h after the administration of omeprazole. Plasma was separated immediately and kept at –30°C until analysis.

Assay

Plasma concentrations of omeprazole and its metabolites, 5-hydroxyomeprazole and omeprazole sulphone were determined by HPLC methods described by Kobayashi *et al.* [23] with minor modification. The method was validated for the concentration range 10–10000 ng ml^{–1}. Intra- and inter-day relative standard deviations were less than 8.9% at the concentration 10 ng ml^{–1}. The limit of quantification was 10 ng ml^{–1} for each compound.

Plasma concentrations of fluvoxamine were determined by HPLC methods developed in our laboratory.

In brief, all solvents used were of HPLC grade (Wako Pure Chemical Industries, Kyoto, Japan). All reagents were purchased from Wako Pure Chemical Industries (Kyoto, Japan). After sample alkalization with 0.5 ml of NaOH (2.5 M), the test compound and internal standard, alprazolam, were extracted from 1000 µl of plasma using 4000 µl of chloroform-*n*-heptane (30 : 70, v/v). The organic phase was evaporated to dryness and the residue was dissolved with 800 µl of mobile phase. An aliquot (500 µl) of the solution was injected into a C₁₈ STR ODS-II analytical column (5 µl, 150 x 4.6 mm I.D.). The mobile phase consisted of phosphate buffer (0.02 M, pH 4.6), perchloric acid (6 M) and acetonitrile (58.93 : 0.07 : 41, v/v) for fluvoxamine and was delivered at a flow rate of 0.6 ml min⁻¹. The peak was detected using a UV detector set at 254 nm for fluvoxamine. The method was validated for the concentration range 1–100 ng ml⁻¹, and good linearity ($r > 0.999$) was confirmed. Intra- and inter-day coefficient variations were less than 7.6% at the concentration 0.8 ng ml⁻¹ for the test compound. Relative errors ranged from –5–10% and mean recoveries were 87–95%. The limit of quantification was 0.8 ng ml⁻¹ for fluvoxamine.

Data analyses of pharmacokinetics

The peak concentration ($C_{\max}$) and concentration peak time ($t_{\max}$) were obtained directly from the original data. The area under the plasma concentration-time curve (AUC(0,8 h)) was calculated with use of the trapezoidal rule. The terminal rate constant (k_e) used for the extrapolation was determined by regression analysis of the log-linear part of the concentration-time curve for each subject. The elimination half-life was determined by $0.693/k_e$. AUC from zero to infinity (0,∞) was calculated by $AUC(0, \text{last}) + C_{\text{last}}/k_e$, where C_{last} is last detectable plasma drug concentration.

Statistical analyses

The paired *t*-test for the comparison of placebo vs fluvoxamine treatment was conducted on pharmacokinetic parameters, while Wilcoxon signed-rank test was performed on the parameter $t_{\max}$. Percentages of placebo in pharmacokinetic parameters between the three genotype groups were compared using one-way ANOVA followed by Scheffe test, whereas percentages of placebo in parameter $t_{\max}$ were compared using the Kruskal–Wallis test. The comparison between the AUC of omeprazole during fluvoxamine coadministration in homozygous and heterozygous EMs groups, and during placebo administration in PMs was performed with the use of one-way ANOVA followed by Scheffe test. Corre-

lations between the percentage of placebo AUC of omeprazole during fluvoxamine and AUC ratio of 5-hydroxyomeprazole : omeprazole were tested using Spearman rank test. A *P* value of 0.05 or less was regarded as significant. SPSS 8.0.1 for Windows (SPSS Japan Inc., Tokyo) was used for these statistical analyses.

Results

Although none of the subjects needed to be withdrawn from this study, mild to moderate side-effects were observed during fluvoxamine administration: mild to moderate nausea in six subjects, mild appetite loss in three subjects, mild drowsiness in five subjects, dry mouth in two subjects. These side-effects continued until day 6 and ameliorated the day after discontinuation of fluvoxamine. No adverse events were reported during placebo administration or after omeprazole plus placebo administration.

No differences between the CYP2C19 genotypes, homozygous EMs, heterozygous EMs and PMs were found in subject profiles, including age (mean ± SD, 25 ± 3, 26 ± 4 and 30 ± 6 years, $P = 0.135$), body weight (66 ± 14, 61 ± 15 and 62 ± 12 kg, $P = 0.807$) and genders (M/F; 5/1, 5/1 and 4/2). Geometric mean (95% confidence interval) of trough plasma concentrations of fluvoxamine on day 6 were 19.8 (4.9, 44.9) in homozygous EMs, 21.4 (11.8, 41.3) in heterozygous EMs, and 19.2 (14.4, 39.2) ng ml⁻¹ in PMs, respectively, which did not differ between CYP2C19 genotypes ($P = 0.902$).

Plasma concentration-time curves of omeprazole during both phases in each genotype group for CYP2C19 are shown in Figure 1. Compared with control, fluvoxamine treatment increased $C_{\max}$ of omeprazole by 3.7-fold (95%CI, 2.4, 5.0-fold, $P < 0.01$) and 2.0-fold (1.4, 2.6-fold, $P < 0.01$), AUC(0,8 h) by 6.0-fold (3.3, 8.7-fold, $P < 0.001$) and 2.4-fold (1.7, 3.2-fold, $P < 0.01$), AUC(0,∞) by 6.2-fold (3.0, 9.3-fold, $P < 0.01$) and 2.5-fold (1.6, 3.4-fold, $P < 0.001$) and prolonged $t_{1/2}$ by 2.6-fold (1.9, 3.4-fold, $P < 0.001$) and 1.4-fold (1.02, 1.7-fold, $P < 0.05$), respectively. However, no pharmacokinetic parameters were changed in PMs (Table 1). There were no differences in $t_{\max}$ of omeprazole between the control and fluvoxamine phases in any genotype patterns (Table 1).

There was a significant difference between the control AUC(0,8 h) of omeprazole in PMs during placebo administration and the AUC(0,8 h) of omeprazole after fluvoxamine in homozygous EMs and heterozygous EMs (ANOVA; $P = 0.024$). *Post hoc* analyses revealed significant difference between the AUC(0,8 h) during

Figure 1

Mean plasma concentration-time curves of omeprazole during placebo and fluvoxamine treatment in homozygous extensive metabolizers (EMs) ($n = 6$), heterozygous EMs ($n = 6$) and poor metabolizers (PMs) ($n = 6$) for CYP2C19. Data are shown as mean and bars are SD. Data during control (○); data during fluvoxamine treatment (●)

Table 1

Pharmacokinetic parameters of omeprazole during placebo or fluvoxamine treatment in homozygous EMs, heterozygous EMs and PMs for CYP2C19

		Homozygous EMs ($n = 6$)	<i>P</i> value	Heterozygous EMs ($n = 6$)	<i>P</i> value	PMs ($n = 6$)	<i>P</i> value
$C_{\max}$ (ng ml ⁻¹)	With placebo	900 (617, 1287)	0.007	1648 (949, 2566)	0.009	2991 (2319, 3845)	0.101
	With fluvoxamine	3131 (1968, 4914)		3145 (2612, 3769)		3352 (2607, 4311)	
* $t_{\max}$ (h)	With placebo	1.75 (1.5, 4.0)	0.414	2.5 (1.0, 4.0)	0.059	2.0 (1.5, 4.0)	0.786
	With fluvoxamine	2.0 (1.5, 3.0)		4.0 (1.5, 4.0)		2.0 (1.5, 3.0)	
AUC(0,8 h) (ng ml ⁻¹ h)	With placebo	1481 (667, 2843)	0.001	4225 (2322, 6577)	0.002	11537 (8413, 15548)	0.112
	With fluvoxamine	7911 (5329, 11730)		9567 (8039, 11363)		13940 (10417, 18664)	
AUC(0,8) (ng ml ⁻¹ h)	With placebo	1483 (664, 2858)	0.002	4411 (2511, 6766)	0.001	15044 (10474, 21149)	0.209
	With fluvoxamine	8340 (5533, 12557)		10507 (9082, 12129)		17348 (12171, 24688)	
Elimination half-life (h)	With placebo	0.55 (0.40, 0.76)	< 0.0001	1.08 (0.62, 1.67)	0.049	2.83 (2.12, 3.71)	0.277
	With fluvoxamine	1.39 (1.21, 1.60)		1.43 (1.04, 1.95)		2.59 (1.81, 3.64)	

Data are shown as geometric mean (95% confidence interval); * $t_{\max}$ is given as median (range); *P* values were shown when compared with fluvoxamine.

the placebo phase in PMs and the increased AUC(0,8 h) in homozygous EMs (Scheffe; $P = 0.032$), but not between AUC(0,8 h) during the placebo phase in PMs and increased AUC(0,8 h) in heterozygous EMs (Scheffe; $P = 0.108$).

Although there were almost no changes in pharmacokinetic parameters of the metabolites, 5-hydroxyomeprazole (Table 2) or omeprazole sulphone (Table 3) between control and fluvoxamine phases, the AUC(0,8 h) ratios of 5-hydroxyomeprazole to omeprazole were significantly decreased during fluvoxamine treatment to $17 \pm 5\%$ ($P < 0.05$) in homozygous EMs

and to $49 \pm 15\%$ ($P < 0.01$) in heterozygous EMs (Table 2). In PMs, no pharmacokinetic parameters were changed.

Figure 2 shows the effect of CYP2C19 genotype on the mean fluvoxamine-mediated percent increase in pharmacokinetic parameters such as peak concentration ($C_{\max}$), AUC(0,8 h), and elimination half-life. The fluvoxamine-mediated percent increase in $C_{\max}$ (ANOVA, $P = 0.0005$), AUC(0,8 h) ($P = 0.002$) and elimination half-life ($P < 0.0001$), but not $t_{\max}$ ($P = 0.300$) significantly differed between the three CYP2C19 genotypes. Figure 3 shows the effect of CYP2C19 genotype on the

Table 2

Pharmacokinetic parameters of 5-hydroxyomeprazole during placebo or fluvoxamine treatment in homozygous EMs, heterozygous EMs and PMs for CYP2C19

		Homozygous EMs (n = 6)	P value	Heterozygous EMs (n = 6)	P value	PMs (n = 6)	P value
$C_{\max}$ (ng ml ⁻¹)	With placebo	277 (165, 474)	0.011	340 (269, 486)	0.856	54 (33, 84)	0.098
	With fluvoxamine	154 (68, 325)		358 (292, 437)		74 (31, 158)	
* $t_{\max}$ (h)	With placebo	1.75 (1.0, 4.0)	0.854	2.5 (1.5, 6.0)	0.917	3.5 (2.0, 6.0)	0.129
	With fluvoxamine	2.0 (1.5, 3.0)		4.0 (1.5, 4.0)		3.5 (2.0, 4.0)	
AUC(0,8 h) (ng ml ⁻¹ h)	With placebo	586 (362, 978)	0.972	1083 (844, 1286)	0.560	262 (152, 422)	0.145
	With fluvoxamine	540 (262, 1072)		1201 (1025, 1405)		304 (139, 602)	
AUC ratio to omeprazole	With placebo	0.39 (0.20, 0.85)	0.019	0.25 (0.19, 0.32)	0.006	0.017 (0.009, 0.030)	0.736
	With fluvoxamine	0.07 (0.03, 0.13)		0.11 (0.10, 0.12)		0.018 (0.011, 0.030)	

Data are shown as geometric mean (95% confidence interval); * $t_{\max}$ is given as median (range); P values were shown when compared with fluvoxamine.

Table 3

Pharmacokinetic parameters of omeprazole sulphone during placebo or fluvoxamine treatment in homozygous EMs, heterozygous EMs and PMs for CYP2C19

		Homozygous EMs (n = 6)	P value	Heterozygous EMs (n = 6)	P value	PMs (n = 6)	P value
$C_{\max}$ (ng ml ⁻¹)	With placebo	82 (42, 149)	0.061	160 (89, 201)	0.025	274 (215, 347)	0.156
	With fluvoxamine	133 (80, 213)		316 (203, 483)		316 (198, 493)	
* $t_{\max}$ (h)	With placebo	2.5 (1.5, 4.0)	0.257	3.5 (3.0, 8.0)	0.083	7.0 (4.0, 8.0)	0.783
	With fluvoxamine	3.0 (3.0, 4.0)		6.0 (4.0, 8.0)		6.0 (4.0, 8.0)	
AUC(0,8 h) (ng ml ⁻¹ h)	With placebo	245 (107, 528)	0.012	758 (326, 970)	0.009	1442 (991, 2047)	0.062
	With fluvoxamine	717 (439, 1154)		1527 (962, 2376)		1710 (1114, 2590)	
AUC ratio to omeprazole	With placebo	0.16 (0.10, 0.26)	0.015	0.17 (0.12, 0.26)	0.340	0.10 (0.06, 0.15)	0.805
	With fluvoxamine	0.09 (0.07, 0.11)		0.15 (0.11, 0.20)		0.10 (0.06, 0.15)	

Data are shown as geometric mean (95% confidence interval). * $t_{\max}$ is given as median (range). P values were shown when compared with fluvoxamine.

mean fluvoxamine-mediated percent decrease in the AUC(0,8 h) ratio of 5-hydroxyomeprazole to omeprazole and the AUC(0,8 h) ratio of omeprazole sulphone to omeprazole. There was also a significant difference in the percent decrease in the AUC ratio of 5-hydroxyomeprazole to omeprazole between CYP2C19 genotypes ($P < 0.0001$), but not in the percent decrease in AUC(0,8 h) ratio of omeprazole sulphone to omeprazole ($P = 0.079$). The results of *post hoc* (Scheffe test) analyses are shown in Figures 2 and 3.

There was a significant correlation between the fluvoxamine-mediated percent increase in AUC(0,8 h) of

omeprazole and the AUC ratio of 5-hydroxyomeprazole to omeprazole ($r_s = 0.886$, $P < 0.001$).

Discussion

Fluvoxamine has been regarded as a potent inhibitor of CYP1A2 [7–15], based on several drug–drug interaction studies. However, it is unlikely that the inhibitory effect of fluvoxamine on CYP1A2 had a significant effect upon the interaction in this study because the major enzyme catalyzing omeprazole metabolism is not CYP1A2, but CYP2C19 and CYP3A4.

Figure 2

Effect of CYP2C19 genotype on the mean fluvoxamine-mediated percent increase in pharmacokinetic parameters such as peak concentration (C_{max}), area under concentration-time curve (AUC) and elimination half-life. Error bars indicate SD

Figure 3

Effect of CYP2C19 genotype on the mean fluvoxamine-mediated percent decrease in the AUC ratio of 5-hydroxyomeprazole to omeprazole and the AUC ratio of omeprazole sulphone to omeprazole. Error bars indicate SD

The present study showed that a low dose of fluvoxamine (50 mg daily) significantly increased plasma omeprazole concentrations in both homozygous EMs and heterozygous EMs of CYP2C19, which is in line with our previous report [18]. Moreover, a pronounced reduction of the AUC ratio of 5-hydroxyomeprazole to omeprazole, which is regarded as an index of CYP2C19 activity, was found in homozygous EMs and heterozygous EMs. Therefore, this study confirms that fluvoxamine is a potent inhibitor of CYP2C19 in EMs of CYP2C19. On the other hand, in PMs, no difference in plasma concentration of omeprazole or the AUC ratio of 5-hydroxyomeprazole to omeprazole was found between control and fluvoxamine. This is a reasonable finding because CYP2C19, which fluvoxamine is expected to inhibit, has no activity in PMs. Based on these results in EMs and PMs therefore we concluded that the inhibitory effect of fluvoxamine on omeprazole metabolism was different between EMs and PMs. This phenomenon is in accordance with previous reports [24, 25].

There was a significant difference between the $AUC(0,8\text{ h})$ during placebo in PMs and the increased $AUC(0,8\text{ h})$ in homozygous EMs, but not between $AUC(0,8\text{ h})$ during placebo in PMs and the increased $AUC(0,8\text{ h})$ in heterozygous EMs. These findings were contrary to our expectations. Since the inhibitory effect of fluvoxamine occurs in a dose-dependent manner [18], pretreatment with 50 mg fluvoxamine daily for 5 days might not fully inhibit CYP2C19 activity in homozygous EMs, but it completely inhibited the CYP2C19 activity in heterozygous EMs, which is lower than that in homozygous EMs.

The fluvoxamine-mediated percent increase in pharmacokinetic parameters of omeprazole except t_{max} and

the percent decrease in the AUC ratio of 5-hydroxyomeprazole to omeprazole significantly differed between the three CYP2C19 genotypes (Figure 2). Furthermore, a significant correlation between the percentage of control in AUC of omeprazole and the AUC ratio of 5-hydroxyomeprazole to omeprazole was found. These findings suggest that the inhibitory effect of fluvoxamine occurs in a gene-dose-dependent manner and is clearly influenced by CYP2C19 activity.

A recent *in vitro* study has shown some involvement of P-glycoprotein in omeprazole transport [26], while an *in vitro* study with cell lines has recently demonstrated that the inhibitory effect of fluvoxamine on P-glycoprotein is intermediate [27]. Therefore, these findings imply possible mechanisms other than CYP2C19 inhibition. The bioavailability of omeprazole might, to some extent, be increased through inhibition of omeprazole transporting back to the intestinal lumen after absorption by fluvoxamine treatment, though the contribution of P-glycoprotein to omeprazole disposition and the inhibitory effect of fluvoxamine on P-glycoprotein is under further *in vivo* investigation.

The increased AUC of omeprazole during fluvoxamine treatment in heterozygous EMs similar to that during placebo in PMs has significant clinical implications, although the increased AUC in homozygous EMs was still significantly lower than the AUC in PMs. Several studies have suggested that the CYP2C19 genotype influences the cure rate of gastric acid-related disorders including eradication rate of *H. pylori* [28–32]. PMs for CYP2C19 have significantly higher eradication rates of *H. pylori* following treatment with such proton pump inhibitors as omeprazole, lansoprazole and rabeprazole than do EMs [28–31]. Therefore, the combination therapy of omeprazole and low dose of fluvoxamine may be helpful in the treatment of acid-related disorders. In addition, lack of major changes in AUC of omeprazole during fluvoxamine treatment in PMs suggests that co-administration of low-dose fluvoxamine does not influence outcomes in the treatment of acid-related disorders in PMs. If CYP2C19 genotype is not available, co-administration of low-dose fluvoxamine may be safer than increasing the omeprazole dose because low-dose fluvoxamine increases omeprazole exposure selectively in EMs, but not in PMs. However, further study is necessary to determine whether or not co-administration of low dose of fluvoxamine is clinically relevant as adjunctive therapy for eradication of *H. pylori* because several subjects suffered from side-effects probably caused by low dose of fluvoxamine treatment in the present study.

Although no side-effects due to the increased omeprazole exposure during the fluvoxamine administration

were observed under the conditions of this study, repeated administration of both omeprazole and fluvoxamine might cause some adverse reaction to omeprazole. Furthermore, adverse reactions to fluvoxamine itself (e.g. serotonin toxicity) should be carefully monitored when clinical doses of these drugs are concomitantly prescribed.

In conclusion, even a low dose of fluvoxamine increased omeprazole exposure in EMs, but did not increase omeprazole exposure in PMs. The increased AUC(0,8 h) in heterozygous EMs was similar to that in PMs. These findings confirm a potent inhibitory effect of fluvoxamine on CYP2C19 activity.

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