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Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status

Tsukasa Uno,[1,2] Mikiko Shimizu,[1] Norio Yasui-Furukori,[1,3] Kazunobu Sugawara[2] & Tomonori Tateishi[1]

[1]*Department of Clinical Pharmacology, Hirosaki University School of Medicine,* [2]*Department of Pharmacy, Hirosaki University Hospital and* [3]*Department of Neuropsychiatry, Hirosaki University School of Medicine, Japan*

Correspondence
Dr Tsukasa Uno, Department of Clinical Pharmacology, Hirosaki University, School of Medicine, Hirosaki 036–8562, Japan.
Tel: 81 172 39 5352
Fax: 81 172 39 5352
E-mail: uno-hki@umin.ac.jp

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Aims
Rabeprazole is known to be a substrate of CYP2C19. Our objective was to evaluate the possible effect of an inhibitor of CYP2C19, fluvoxamine, and compare the inhibitory effect of fluvoxamine on the metabolism of rabeprazole between CYP2C19 genotypes.

Methods
A two-way randomized double-blind, placebo-controlled crossover study was performed. Twenty-one volunteers, of whom seven were homozygous extensive metabolizers (EMs), eight were heterozygous EMs and six were poor metabolizers (PMs) for CYP2C19, received two 6-day courses of either fluvoxamine 50 mg or placebo daily in a randomized fashion with a single oral dose of rabeprazole 20 mg on day 6 in all cases. Plasma concentrations of rabeprazole and its metabolite rabeprazole thioether were monitored up to 24 h after dosing.

Results
During placebo administration, the mean AUCs(0,∞) of rabeprazole in homozygous EMs, heterozygous EMs and PMs were 882 (95% CI, 602, 1162) ng ml^{-1}h , 1214 (975, 1453) ng ml^{-1} h and 2762 (2482, 3042) ng ml^{-1} h ($P < 0.001$), respectively. Fluvoxamine treatment increased AUC(0,∞) of rabeprazole and rabeprazole thioether by 2.8-fold ($P < 0.001$) and 5.1-fold ($P < 0.01$) in homozygous EMs, and by 1.7-fold ($P < 0.01$) and 2.6-fold ($P < 0.01$) in heterozygous EMs, and significantly prolonged the elimination half-life of rabeprazole and rabeprazole thioether in homozygous EMs and in heterozygous EMs, whereas no difference in any pharmacokinetic parameters was found in PMs. There was a significant difference in fluvoxamine-mediated percentage increase in AUC(0,∞) of rabeprazole and rabeprazole thioether between CYP2C19 genotypes.

Conclusions
The present study indicates that there are significant drug interactions between rabeprazole and fluvoxamine in EMs of CYP2C19. It is predominantly involved in rabeprazole and rabeprazole thioether metabolism in EMs. Therefore, CYP2C19 is the key determinant of rabeprazole disposition in EMs.

Introduction

Rabeprazole, which is structurally related to omeprazole, is a substituted benzimidazole, and acts as a proton pump inhibitor (PPI) that suppresses gastric acid secretion through an interaction with (H^+/K^+)-ATPase in gastric parietal cells. Like other PPIs (omeprazole, lansoprazole and pantoprazole), rabeprazole is effective in the treatment of various peptic diseases, including

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gastric and duodenal ulcer, gastroesophageal reflux disease and Zollinger–Ellison syndrome [1, 2].

Cytochrome P450 (CYP) 3A4 and polymorphic CYP2C19 are involved in the metabolism of PPIs [3, 4]. In individuals who are poor metabolizers (PMs) of CYP2C19, the area under the concentration-time curve (AUC) of PPIs is markedly increased and the pharmacodynamic effects of PPIs (e.g. omeprazole and lansoprazole) are enhanced in comparison with those in heterozygous extensive metabolizers (EMs) or homozygous EMs [5, 6]. Nonenzymatic reduction of rabeprazole to rabeprazole thioether is reported to be a major pathway in the metabolism of rabeprazole, but the contribution of CYP2C19 is considered to be smaller, compared with the metabolism of omeprazole or lansoprazole [4, 7, 8]. However, several recent reports have indicated that rabeprazole plasma concentrations differ significantly among the different CYP2C19 genotypes (i.e. highest in PMs, intermediate in heterozygous EMs and lowest in homozygous EMs) [9–13] and that acid inhibition by rabeprazole depends on CYP2C19 genotypic status [11–13]. In addition, rabeprazole thioether, which is formed nonenzymatically from rabeprazole, is metabolized to dimethylated thioether-rabeprazole by CYP2C19 [11]. Therefore, CYP2C19 may have an important role in the disposition of both rabeprazole and rabeprazole thioether.

Fluvoxamine, a selective serotonin re-uptake inhibitor (SSRI), is regarded not only as a potent CYP1A2 inhibitor but also as a CYP2C19 inhibitor [14–17]. Recent studies in our laboratory showed that fluvoxamine (50 mg daily) increased the AUC and prolonged elimination half-life of omeprazole [18] and lansoprazole [19] in EMs, but not in PMs. Accordingly, we postulated that fluvoxamine would inhibit rabeprazole metabolism only in EMs.

To date, however, there is no published information indicating a detailed pharmacokinetic drug interaction between rabeprazole and fluvoxamine in humans. Therefore, we intended to examine whether fluvoxamine would really affect the metabolism of rabeprazole and to what extent these possible interactions could occur in relation to the CYP2C19 genotype status.

Methods

Study design

Twenty-one Japanese healthy volunteers (10 males and 11 females) were enrolled in this study. Their mean age was 24.7 ± 4.3 years and mean body weight was 55.4 ± 7.5 kg. The Ethics Committee of Hirosaki University School of Medicine approved the study protocol, and written informed consent was obtained from each participant. The variant alleles for CYP2C19, *CYP2C19*3(*3)* and *CYP2C19*2(*2)* were identified using the PCR-RFLP methods of de Morais *et al.* [20], prior to the study. The CYP2C19 genotype analyses revealed four different patterns: **1/*1* in seven, **1/*2* in five, **1/*3* in three and **2/*2* in six. These were divided into three groups, homozygous EMs (**1/*1*, $n = 7$), heterozygous EMs (**1/*2* and **1/*3*, $n = 8$), and PMs (**2/*2*, $n = 6$).

A randomized double-blind placebo-controlled crossover study design in two phases was conducted at intervals of 2 weeks. Fluvoxamine (25 mg) as the capsule formulation containing a tablet (Luvox®, Fujisawa Pharmaceutical Co., Ltd, Osaka, Japan) or matched placebo (as the capsule formulation with the same appearance and size as that of fluvoxamine) was taken orally twice a day (09.00 h, 21.00 h) for 6 days. Volunteers within each group were allocated to either of two different drug sequences: placebo-fluvoxamine or fluvoxamine-placebo. On day 6, they took a single oral 20 mg dose of rabeprazole (Pariet ®, Eizai Co., Ltd, Tokyo, Japan) and 25 mg of fluvoxamine or placebo with 240 ml of tap water at 09.00 h after an overnight fast. 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 dosing.

Blood sampling

Blood samples (10 ml each) for the determination of rabeprazole and its metabolite rabeprazole thioether were taken into heparinized tubes just before and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after the administration of rabeprazole. Plasma was separated immediately and kept at −30 °C until analysis.

Drug assay

Plasma concentrations of rabeprazole and rabeprazole thioether were quantified using a high performance liquid chromatography (HPLC) method developed in our laboratory [21]. In brief, after alkalization with 1 ml of 0.05 M phosphate buffer adjusted to pH 10.40 with 2.5 M NaOH, 1 ml plasma was extracted with 5 ml of diethyl ether-dichloromethane (90 : 10, v : v). The organic phase was evaporated to dryness at 40 °C. Samples were dissolved into 100 µl of 0.1% diethylamine in methanol and injected into the HPLC system (SHIMADZU CLASS-VP, SHIMADZU Corporation, Kyoto, Japan), with a C18 Grand ODS-80TM TS column (particle size 5 µm, 250 × 4.6 mm I.D., MASIS Inc., Aomori, Japan). The mobile phase consisted of phosphate buffer (0.05 M, pH 7.0), acetonitrile (50 : 50, v : v). The flow rate was 0.8 ml min^{-1} and the wavelength was set at 288 nm. The

limit of quantification was 1 ng ml^{-1} for rabeprazole and 3 ng ml^{-1} for rabeprazole thioether. Intra- and interday relative standard derivatives were less than 4.4 and 5.6% for rabeprazole and 5.0 and 7.2% for rabeprazole thioether, respectively, at the lowest concentrations.

Pharmacokinetic analysis

The peak concentration (C_{max}) and concentration peak time (t_{max}) were obtained directly from the original data. Pharmacokinetic analyses were conducted using a one-compartment model. The terminal rate constant (λ_z) 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 $0.693/\lambda_z$. The area under the plasma concentration-time curve (AUC(0,24 h)) was calculated by the trapezoidal rule. AUC from zero to infinity (0,∞) was calculated by AUC(0,last) + C_{last}/λ_z, where C_{last} is last detectable plasma drug concentration. Total clearance (CL/*F*) was calculated by Dose/AUC (0,∞).

Statistical analyses

One-way ANOVA and Fisher's exact test were used for comparisons between the three CYP2C19 genotypes and clinical profiles such as age, body weight and gender. A paired *t*-test for the comparison of placebo *vs.* fluvoxamine was conducted on pharmacokinetic parameters. Wilcoxon signed-rank test was performed on t_{max} because of non-normalized distribution. Percent changes in pharmacokinetic parameters and AUC ratio of rabeprazole thioether to rabeprazole between the three genotype groups were compared using one-way ANOVA followed by Scheffe's test. Correlation between percent changes in AUC of rabeprazole during fluvoxamine and AUC of rabeprazole, and correlation between the fluvoxamine-mediated percent increase in AUC(0,∞) ratio of rabeprazole thioether : rabeprazole and the AUC(0,∞) ratio of rabeprazole thioether : rabeprazole were tested using the 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 withdrew from the study, the following mild to moderate side-effects were observed during fluvoxamine administration: mild to moderate nausea in two subjects, mild appetite loss in three subjects and mild drowsiness in five 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 rabeprazole plus placebo administration.

No differences between the CYP2C19 genotypes, homozygous EMs, heterozygous EMs and PMs were found for age [mean and 95% confidence interval, 25 (23, 26), 26 (21,31) and 23 (22, 24) years], body weight [56 (51, 60), 58 (51, 64) and 53 (48, 58) kg] and gender (M/F; 3/4, 5/3 and 2/4).

Plasma concentration-time curves of rabeprazole during the two phases for each genotype group are shown in Figure 1, and the pharmacokinetic parameters are summarized in Table 1. During placebo administration, the mean plasma concentrations of rabeprazole and rabeprazole thioether were higher in PMs compared with homozygous EMs and heterozygous EMs (Figure 1). Significant changes were found for C_{max} ($P < 0.01$–0.001), AUC(0,∞) ($P < 0.001$) and elimination half-life ($P < 0.05$–0.001), but not for t_{max} between different CYP2C19 genotypes. The CL/*F* values of rabeprazole and AUC ratio to parent drug for rabeprazole thioether differed between the CYP2C19 genotypes ($P < 0.05$–0.01) (Table 1).

In homozygous EMs, fluvoxamine treatment significantly increased rabeprazole C_{max} and AUC(0, ∞) by 2.0-fold ($P < 0.05$) and 2.8-fold ($P < 0.001$), respectively, and prolonged its elimination half-life by 2.4-fold ($P < 0.05$). In heterozygous EMs, fluvoxamine also increased the AUC of rabeprazole by 1.7-fold ($P < 0.001$) and prolonged its elimination half-life by 1.8-fold ($P < 0.05$). However, no pharmacokinetic parameters of rabeprazole were changed in PMs. Fluvoxamine also increased rabeprazole thioether AUC(0, ∞) by 5.1-fold and 2.6-fold in homozygous EMs ($P < 0.001$) and heterozygous EMs ($P < 0.001$), respectively. No difference was found in the elimination half-life of rabeprazole thioether during fluvoxamine treatment between CYP2C19 genotypes.

There was a significant correlation between the fluvoxamine-mediated percent increase in AUC(0,∞) of rabeprazole and the AUC(0,∞) of rabeprazole ($r_s = 0.731$, $P < 0.001$) as well as between the fluvoxamine-mediated percent increase in AUC(0,∞) ratio of rabeprazole thioether : rabeprazole and the AUC(0,∞) ratio of rabeprazole thioether : rabeprazole ($r_s = 0.572$, $P = 0.0105$).

Discussion

The present study showed significant differences in AUC(0,∞) of rabeprazole between different CYP2C19 genotypes during placebo treatment. The relative values of the AUC(0,∞) of rabeprazole in homozygous EMs, heterozygous EMs and PMs were 1 : 1.4 : 3.1. This is in

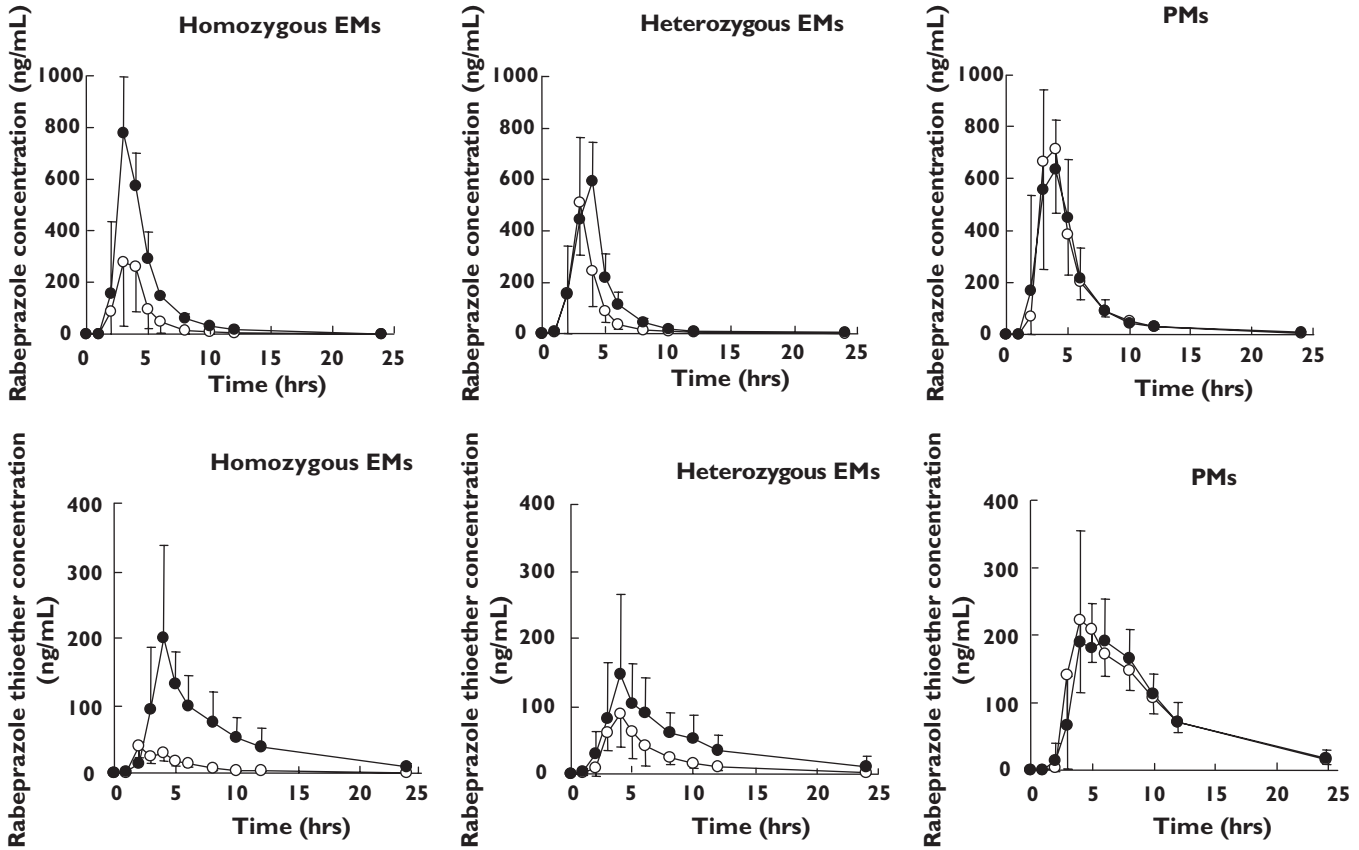

Figure 1

Plasma concentration-time curves of rabeprazole (upper panel) and rabeprazole thioether (lower panel) during placebo and fluvoxamine treatments in homozygous extensive metabolizers (EMs) (n = 7), heterozygous EMs (n = 8), and poor metabolizers (PMs) (n = 6) for CYP2C19. Data are shown as mean and bars are SEM. Open circles and closed circles indicate data during placebo and fluvoxamine treatments, respectively

line with several previous studies [9–13] and indicates that CYP2C19 genotype is a major determinant in rabeprazole disposition.

This is the first report of an effect on rabeprazole disposition in relation to CYP2C19 genotypes. Fluvoxamine is regarded as a potent inhibitor of CYP1A2 and CYP2C19. Previous studies in our laboratory showed that fluvoxamine treatment increased the AUC of PPIs (e.g. omeprazole and lansoprazole) and prolonged elimination half-life of PPIs in homozygous EMs and heterozygous EMs, but not in PMs [18, 19], indicating a potent inhibitory effect of fluvoxamine on CYP2C19 activity. Because CYP1A2 is not involved in rabeprazole metabolism [4], it is unlikely that the inhibitory effect of fluvoxamine on CYP1A2 had a significant effect in this study. As in previous studies [18, 19], fluvoxamine significantly increased the AUC of rabeprazole and prolonged its elimination half-life in homozygous EMs and heterozygous EMs (Table 1). In contrast, in PMs with no CYP2C19 activity, no difference in any pharmacokinetic parameters was found between the placebo and fluvoxamine phases. Therefore, these findings strongly suggest that the mechanism of this drug interaction results in CYP2C19-mediated inhibitory effects by fluvoxamine. Moreover, the inhibitory effect of fluvoxamine on rabeprazole pharmacokinetics showed a similar trend to that reported in previous studies [18, 19]: the inhibitory effect of fluvoxamine was greatest in homozygous EMs, less in heterozygous EMs and least in PMs. In addition, when considering the inhibitory effect of fluvoxamine on the disposition of the three PPIs in EMs, the order is as follows: omeprazole > lansoprazole > rabeprazole, which is plausible because the relative effect of CYP2C19-related polymorphism on the metabolism of the three PPIs is also similar [4].

There was a significant difference in disposition of rabeprazole thioether between different CYP2C19 genotypes during placebo treatment. The relative values of the AUC(0, ∞) of rabeprazole thioether in homozygous

Table 1
Pharmacokinetic parameters of rabeprazole and rabeprazole thioether during placebo or fluvoxamine treatment in homozygous EMs, heterozygous EMs and PMs for CYP2C19

		Homozygous EMs (n = 7)	Heterozygous EMs (n = 8)	PMs (n = 6)
Rabeprazole				
C_{max} (ng ml^{-1})	With placebo	442 (273, 611)***	553 (414, 692)**	967 (783, 1151)
	With fluvoxamine	892 (608, 1176)#	711 (649, 773)	847 (749, 945)
t_{max} (h)[1]	With placebo	3.0 (2.0–4.0)	2.9 (2.0–3.0)	3.5 (3.0–4.0)
	With fluvoxamine	3.7 (3.0–5.0)	3.9 (2.0–8.0)	3.3 (2.0–5.0)
AUC (0,∞) (ng ml^{-1} h)	With placebo	882 (602, 1162)***	1214 (975, 1453)***	2762 (2482, 3042)
	With fluvoxamine	2486 (1786, 3186)*,###	2037 (1755, 2319)**,###	2963 (2800, 3126)
CL/*F* (l kg^{-1} h^{-1})	With placebo	0.50 (0.36, 0.64)***	0.33 (0.29, 0.37)**	0.13 (0.12, 0.14)
	With fluvoxamine	0.18 (0.14, 0.22)###	0.20 (0.16, 0.24)###	0.12 (0.11, 0.13)
Elimination half-life (h)	With placebo	1.3 (0.9, 1.7)**	2.7 (0.9, 4.3)*	4.3 (1.6, 7.0)
	With fluvoxamine	3.1 (1.7, 4.5)#	4.8 (3.1, 6.5)#	5.7 (4.5, 5.9)
Rabeprazole thioether				
C_{max} (ng ml^{-1})	With placebo	68 (42, 94)***	91 (55, 127)***	255 (184, 326)
	With fluvoxamine	222 (142, 302)##	201 (145, 257)	270 (176, 364)
t_{max} (h)[1]	With placebo	4.0 (2.0–5.0)	3.9 (3.0–4.0)	4.3 (3.0–5.0)
	With fluvoxamine	4.3 (4.0–5.0)	5.0 (3.0–10.0)	5.0 (4.0–6.0)
AUC (0,∞) (ng ml^{-1} h)	With placebo	289 (203, 375)***	477 (348, 606)***	2209 (1993, 2425)
	With fluvoxamine	1476 (1080, 1872)**,###	1234 (874, 1594)**,###	2060 (1805, 2315)
Elimination half-life (h)	With placebo	2.8 (2.1, 3.5)***	4.6 (3.5, 5.7)**	5.2 (4.2, 6.2)
	With fluvoxamine	5.8 (5.2, 6.4)##	6.6 (5.0, 8.2)##	5.5 (4.4, 6.6)
AUC ratio to rabeprazole	With placebo	0.38 (0.24, 0.52)**	0.40 (0.36, 0.44)*	0.81 (0.71, 0.91)
	With fluvoxamine	0.64 (0.40, 0.88)##	0.62 (0.46, 0.78)#	0.70 (0.60, 0.80)

*Data are shown as mean and 95% confidence interval. [1]t_{max} is median (range). *P < 0.05, **P < 0.01, ***P < 0.001, compared with PMs, #P < 0.05, ##P < 0.01, ###P < 0.001, compared with placebo.*

EMs, heterozygous EMs and PMs were 1 : 1.7 : 7.6. Rabeprazole thioether is formed via nonenzymatic reduction and is metabolized by CYP2C19 to dimethylated thioether-rabeprazole [11]. In addition, in parallel with the elevation of the plasma concentration of rabeprazole, the inhibitory effect of fluvoxamine on the disposition of rabeprazole thioether differed significantly between the different CYP2C19 genotypes. CYP2C19, therefore, would play a more major role in the disposition of the thioether than it would for the parent drug rabeprazole, because the relative values of the AUC(0,∞) of rabeprazole were 1 : 1.4 : 3.1 in homozygous EMs, heterozygous EMs and PMs, as stated earlier.

Several studies have suggested that CYP2C19 genotype influences the cure rate of gastric acid-related disorders including eradication rate of *H. pylori*. PMs for CYP2C19 have significantly higher eradication rates of *H. pylori* following treatment with such proton pump inhibitors as omeprazole [22], lansoprazole [23] and rabeprazole [24] than do EMs. Moreover, different dosage regimens of rabeprazole for gastro-oesophageal reflux disease therapy between different CYP2C19 genotypes have been demonstrated in relation to lower plasma concentration and a shorter time-dependent effect in homozygous EMs and heterozygous EMs compared with that in PMs [9, 13, 25]. Therefore, the increased AUC(0, ∞) and prolonged elimination half-life of rabeprazole in homozygous and heterozygous EMs during fluvoxamine treatment might be helpful in the treatment of acid-related disorders. However, fluvoxamine co-administration induces many adverse events, albeit mild ones, and therefore other possibilities such as administering rabeprazole four times daily [12] or a concomitant dosage regimen of a histamine H_2-receptor blocker with rabeprazole [25] are proposed to avoid the CYP2C19 polymorphism effect in PPI therapy. Shortening of the dosage interval leads to sufficient acid suppression in EMs.

In conclusion, the present study indicates there are significant drug interactions between rabeprazole and fluvoxamine in EMs of CYP2C19. CYP2C19 is predominantly involved in rabeprazole and rabeprazole

thioether metabolism in EMs and therefore, it is the key determinant of rabeprazole disposition in EMs.

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