Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19)

Objectives: **Fluvoxamine is metabolized by the polymorphic cytochrome P450 (CYP) 2D6 and the smoking-inducible CYP1A2. Therapeutic doses of fluvoxamine inhibit both CYP1A2 and CYP2C19. In this study we used extensive metabolizers (EMs) and poor metabolizers (PMs) of debrisoquin (INN, debrisoquine) (CYP2D6) and two probes, caffeine (CYP1A2) and omeprazole (CYP2C19), to investigate whether nontherapeutic doses of fluvoxamine inhibit CYP1A2 but possibly not CYP2C19.**

Methods: **Single oral doses of 100 mg caffeine and 20 mg omeprazole were given separately to 5 EMs and 5 PMs of debrisoquin to assess the activity of CYP1A2 and CYP2C19, respectively. Initially, a single oral dose of fluvoxamine (25 mg to PMs and 50 mg to EMs) was given, followed by 1 week of daily administration of 25 mg × 2 to EMs and 25 mg × 1 to PMs. Caffeine (day 6) and omeprazole (day 7) were again administered at the steady state of fluvoxamine. Later the study protocol was repeated with a lower dose of fluvoxamine, 10 mg × 2 to EMs and 10 mg × 1 to PMs for 1 week. Concentrations of fluvoxamine, caffeine, omeprazole, and their metabolites were analyzed by HPLC methods in plasma and urine.**

Results: **The kinetics of fluvoxamine were not significantly different in EMs and PMs after a single oral dose of the drug. At the higher but not the lower steady-state dose of fluvoxamine, a significantly lower clearance in PMs compared with EMs was observed (geometric mean, 0.86 versus 1.4 L/h per kilogram; $P < .05$). At steady state, the 25 mg × 1 or × 2 fluvoxamine dose caused a pronounced inhibition of about 75% to 80% for both CYP1A2 and CYP2C19, whereas the inhibition after the lower 10 mg × 1 or × 2 dose was about 40% to 50%. The area under the plasma concentration–versus–time curve from 0 to 24 hours [AUC(0-24)] of caffeine increased 5-fold ($P < .001$) after the higher dose of fluvoxamine and 2-fold ($P < .05$) after the lower dose. The area under the plasma concentration–time curve from time zero to 8 hours [AUC(0-8)] ratio of 5-hydroxyomeprazole/omeprazole decreased 3.4-fold ($P < .001$) and 2.4-fold ($P < .001$), respectively. One EM subject had a very low oral clearance of fluvoxamine after both single and multiple dosing of the drug. This subject might have a deficient transporter protein in the gut, leading to an increased absorption of fluvoxamine.**

Conclusion: **No convincing evidence was found that CYP2D6 is an important enzyme for the disposition of fluvoxamine. Other factors seem to be more important. A nontherapeutic oral daily dose of fluvoxamine is sufficient to provide a marked inhibition of both caffeine (CYP1A2) and omeprazole (CYP2C19) metabolism. It was not possible to separate the inhibitory effects of fluvoxamine on these enzymes, even after such a low daily dose such as 10 mg × 1 or × 2 of fluvoxamine. (Clin Pharmacol Ther 2002;71:141-52.)**

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Supported by grants from the Swedish Foundation for Strategic Research (Stockholm), the National Institute of General Medical Sciences, National Institutes of Health (Bethesda, Md)(grant No. 1R01 GM60548-01A2), the Swedish Medical Research Council (grant No. 3902), the Karolinska Institutet, the Uehara Memorial Foundation, Japan (grant No. 00/0034/01), the Fondo de Investigacion Sanitaria, Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo (Madrid), the Junta de Extremadura (Mérida, Spain) (grant IPR00C054), the Convenio de Farmacovigilancia, Consejeria de Sanidad (Junta de Extremadura, Mérida, Spain), and the Universidad de Extremadura (Badajoz). This study was carried out in coordination with COST B15 from the European Union.

Received for publication June 18, 2001; accepted Nov 19, 2001.

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009-9236/2002/$35.00 + 0 **13/1/121788**

doi:10.1067/mcp.2002.121788

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The antidepressant fluvoxamine belongs to the group of selective serotonin reuptake inhibitors (SSRIs). Fluvoxamine is metabolized in the liver by the cytochrome P450 (CYP) enzymes CYP2D6 and CYP1A2.[1-3] The drug is a potent inhibitor of CYP1A2 and, therefore, causes pharmacokinetic interactions with drugs metabolized by this enzyme.[4] The metabolism of many drugs such as amitriptyline,[5] caffeine,[6] clomipramine,[5,7] clozapine,[8,9] imipramine,[10,11] olanzapine,[12] and theophylline[13] is inhibited by fluvoxamine. It is well established that smoking induces the metabolism of drugs catalyzed by CYP1A2, and therefore smokers have lower plasma concentrations compared with nonsmokers.[1,3,14] Some studies have also located a gender difference, with a decreased CYP1A2 activity in female subjects compared with male subjects.[15,16] However, confirmation that this gender difference is not due to the intake of oral contraceptives is needed.[17,18] The metabolism of fluvoxamine involves saturation kinetics, described with therapeutic doses.[19,20]

Furthermore, fluvoxamine has been found to be a moderate inhibitor of CYP2C19.[21] Thus clinical drug interactions between fluvoxamine and substrates of CYP2C19 such as citalopram,[22] omeprazole,[23] and chloroguanide hydrochloride (INN, proguanil)[24] may also be of importance. Another clinically important interaction is between fluvoxamine and warfarin,[25] a substrate of CYP2C9.[26] A recent study seems to confirm that fluvoxamine is also a weak inhibitor of CYP2C9 at daily doses of 75 mg.[27]

Caffeine is predominantly eliminated by CYP1A2 via *N*-3-demethylation to paraxanthine.[28] The further metabolism of caffeine involves other enzymes such as *N*-acetyltransferase and CYP2E1.[29] Several publications have evaluated the use of caffeine as a probe for CYP1A2 activity.[30-32] In a previous study it was confirmed that the urinary *N*-3-demethylated caffeine metabolites divided by caffeine strongly correlated with the plasma caffeine clearance, regarded as the criterion standard for the measurement of CYP1A2 activity.[33]

The proton pump inhibitor omeprazole is completely metabolized, mainly by hydroxylation catalyzed by CYP2C19.[34] The rate of hydroxylation correlates with the hydroxylation of *S*-mephenytoin and can be used to assess the activity of CYP2C19.[35,36] Omeprazole is also, to a minor extent, metabolized by CYP3A4 to omeprazole sulfone.[23,37] In poor metabolizers (PMs) of *S*-mephenytoin, this is the predominant metabolic pathway.[37] The sulfone is subsequently hydroxylated by CYP2C19. Limited evidence suggests that fluvoxamine has an inhibitory effect on CYP3A4, measured as increased plasma concentrations of alprazolam[38] and cyclosporine (INN, ciclosporin)[39] during fluvoxamine coadministration. Thus a decreased formation of omeprazole sulfone is possible in combination with fluvoxamine.

Selective inhibitors of different CYPs can be used in the experimental design of clinical studies. Quinidine[40] and sulfaphenazole[41] are potent and selective in vivo inhibitors of CYP2D6 and CYP2C9, respectively. The aim of this study was to discover whether low doses of fluvoxamine in vivo could be used as selective inhibitors of CYP1A2. In vivo studies have described an inhibition of both CYP1A2 and CYP2C19 by fluvoxamine given in therapeutic doses.[42] Results from in vitro studies with the use of human liver microsomes indicate that clozapine *N*-demethylation is inhibited by fluvoxamine. This is partly due to the inhibition of CYP isoforms, with CYP1A2 and CYP2C19 being the most sensitive, with inhibition constant (K_i) values of 0.041 μmol/L and 0.087 μmol/L, respectively. The K_i values of other CYP enzymes (ie, CYP2C9, CYP2D6, and CYP3A4) were higher (ie, 2.2 μmol/L, 4.9 μmol/L, and 24 μmol/L, respectively).[43] However, this in vitro study does not give any information about effects seen in vivo.

To test our hypothesis that low doses of fluvoxamine may be used to specifically inhibit CYP1A2 but not CYP2C19, we performed an interaction study between fluvoxamine and the probe drugs caffeine (CYP1A2) and omeprazole (CYP2C19) in nonsmokers phenotyped as extensive metabolizers (EMs) or PMs of debrisoquin (INN, debrisoquine). Because fluvoxamine kinetics is partly dependent on the polymorphic enzyme CYP2D6,[1] we gave double the dose of fluvoxamine to EMs of debrisoquin compared with PMs of debrisoquin to obtain similar plasma concentrations of fluvoxamine.

SUBJECTS AND METHODS

Subjects. Twelve healthy white subjects, 6 men and 6 women, aged 22 to 45 years (mean, 30 years) and

	Period 1			Period 2			Period 3		
	Single dose			Multiple doses			Multiple doses		
	day 1	day 2	day 3	days 1-5	day 6	day 7	days 1-5	day 6	day 7
Caffeine	100 mg			100 mg			100 mg		
Omeprazole		20 mg				20 mg			20 mg
Fluvoxamine			50 mg to EM 25 mg to PM	25 mg x2 to EM 25 mg x1 to PM			10 mg x2 to EM 10 mg x1 to PM		

Fig 1. Study design. Single doses of fluvoxamine, caffeine, and omeprazole were given during period 1. Subjects took a higher fluvoxamine dose for 5 days before caffeine and omeprazole were given again during steady-state conditions of fluvoxamine (period 2). During a third period, the protocol of period 2 was repeated but with a lower dose of fluvoxamine. EMs, Extensive metabolizers of debrisoquin; PMs, poor metabolizers of debrisoquin (CYP2D6).

weighing 56 to 94 kg (mean, 81 kg for the men and 69 kg for the women), participated in this study, which included 7 EMs and 5 PMs of debrisoquin. The debrisoquin metabolic ratio (MR) ranged from 0.57 to 2.2 in EMs and from 35 to 260 in PMs. Genotyping of CYP2D6 and CYP2C19 was performed in 1 subject (subject No. 12) by the methods of Heim and Meyer[44] (*CYP2D6*3* and **4*) and de Morais et al[45] (*CYP2C19*2*). All subjects were healthy as assessed by medical history, physical examination, urine drug screen, standard 12-lead electrocardiogram, virologic testing (hepatitis B, hepatitis C, human immunodeficiency virus), and routine laboratory analyses (liver and kidney function and hematologic testing). All were nonsmokers and had been drug-free for at least 1 week before the study. The consumption of alcohol was prohibited 48 hours before and throughout the study. No caffeine-containing products (coffee, tea, cola, chocolate) were allowed within 36 hours before and 24 hours after caffeine intake. The use of oral contraceptives was allowed, and 1 woman took a combination of 0.15 mg desogestrel and 20 μg ethinyl estradiol (INN, ethinylestradiol).

The Human Ethics Committee at Huddinge University Hospital, Karolinska Institutet, approved the study protocol. Written informed consent was obtained from all subjects. They were free to withdraw from the study at any time.

Study design. The study was performed in 3 periods (Fig 1). The first day of period 1, a single oral dose of 100 mg caffeine (tablet Koffein; Recip AB, Stockholm, Sweden) and the second day a single dose of 20 mg omeprazole (capsule Losec; Astra Hässle AB, Mölndal, Sweden) were given to all subjects. On the third day the 5 EMs received 50 mg (25 mg × 2) and 5 PMs received 25 mg fluvoxamine as a single oral dose. Fluvoxamine was administered as 25-mg capsules manufactured by the Pharmacy at Huddinge University Hospital. For this purpose the 50 mg tablet (Fevarin; Meda AB, Stockholm, Sweden) was used. All drugs were given at 8 AM after an overnight fast for at least 8 hours.

During the second study period, the volunteers took multiple doses of fluvoxamine, 25 mg daily given at 8 AM to 5 PMs and 25 mg twice a day given at 8 AM and 8 PM to 5 EMs for 7 days, to reach steady-state concentrations of fluvoxamine (Fig 1). The volunteers took their medications at home. Side effects were documented by the volunteers and were asked for at the trial unit during the study days. On days 6 and 7, single doses of caffeine (100 mg) and omeprazole (20 mg) were given according to the same protocol as during period 1. Period 2 was performed 2 to 16 days after period 1.

Because the fluvoxamine dose given during period 2 strongly inhibited both CYP1A2 and CYP2C19 (see Results), a lower dose of fluvoxamine was given during period 3. This was performed 3.4 to 5.8 months after period 2. The third period was identical to the second period, but a lower dose of fluvoxamine was given (ie, 10 mg daily to PMs and 20 mg [10 mg × 2] to EMs) (Fig 1). Again, 10- mg fluvoxamine capsules were manufactured by the hospital pharmacy as described. Two EM subjects (subjects No. 1 and No. 4) were not able to participate in period 3 because of travel abroad and, therefore, were replaced by 2 new EMs (subjects No. 12 and No. 13). They also followed the protocol in period 1 before entering period 3.

Blood and urine sampling. Standardized lunch and dinner were served during days 1 to 3 in period 1 and days 6 to 7 in periods 2 and 3, with the first meal served at 3 hours after drug intake. Venous blood samples (10 ml) were drawn at 0, 2, 4, 6, 8, 10, and 24 hours after caffeine administration and at 0, 1, 2, 3, 4, 6, and 8 hours after omeprazole intake. Blood samples for flu-

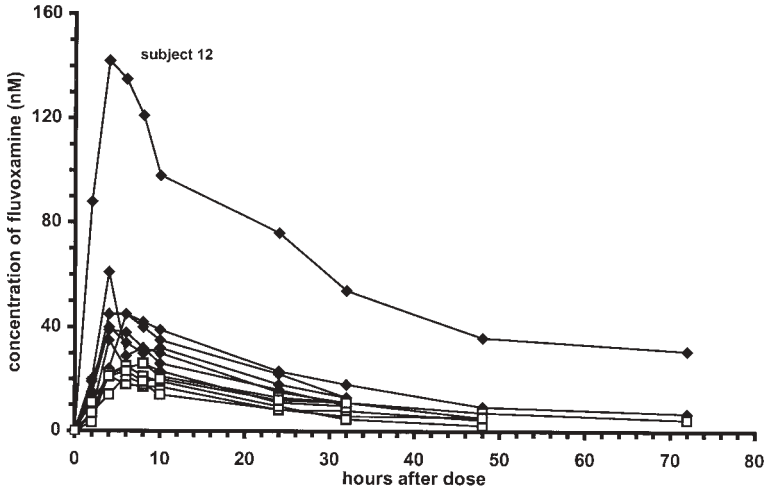

Fig 2. Individual fluvoxamine plasma concentrations over time after a single oral fluvoxamine dose of 25 mg in PMs *(open squares)* and 50 mg in EMs *(solid diamonds)*.

voxamine analysis during period 1 were obtained at the same time points as for caffeine but extended with samples at 32, 48, and 72 hours after fluvoxamine intake, with the last two samples only in PMs. The blood sampling protocol for caffeine and omeprazole on days 6 and 7 during the multiple doses of fluvoxamine in study periods 2 and 3 was identical to that of period 1. The blood samples for fluvoxamine analysis during periods 2 and 3 were drawn at trough level (just before the morning dose) on days 6 and 7, followed by samples at 2, 4, 6, 8, 10, and 12 hours after dose intake on day 7. After centrifugation, plasma was separated and stored frozen at –20°C until analysis. All urine was collected for 24 hours after caffeine intake. The urine volume was measured and the pH was adjusted to 3.5 with concentrated hydrochloric acid. Aliquots of 10 ml were stored at –20°C until analyzed.

Drug analysis. Quantification of fluvoxamine in plasma was performed with HPLC and ultraviolet detection as described by Carrillo et al.[1] The limit of quantification was 2.5 nmol/L. The intra-assay and interassay coefficients of variation (CV) were 5.2% and 4.7%, respectively, at a fluvoxamine concentration of 10 nmol/L and 4.6% and 3.1%, respectively, at a fluvoxamine concentration of 50 nmol/L.

The plasma concentrations of omeprazole and its two metabolites 5-hydroxyomeprazole and omeprazole sulfone were quantified with the use of a reversed-phase HPLC method similar to that described by Tybring et al.[36] The intra-assay and interassay CV values for omeprazole and the two metabolites were lower than 6.6% in the range from 100 to 1000 nmol/L. The limits of quantification were 25 nmol/L for omeprazole and the sulfone and 50 nmol/L for 5-hydroxyomeprazole. The 5-hydroxyomeprazole/omeprazole area under the concentration-time curve [AUC(0-8 h)] ratio was used as a measure of the CYP2C19 activity.[36] Similarly, the omeprazole sulfone/omeprazole AUC(0-8 h) ratio was used as a measure of the activity of CYP3A4.[37]

Caffeine and metabolites in plasma and urine were measured by HPLC according to Carrillo et al.[33] In plasma, only caffeine (137X) was measured. The limit of quantification was 0.15 μmol/L. The magnitudes of the intra-assay and interassay CV values were consistent with those previously published.[33] The 24-hour urinary caffeine *N*-3-demethylation index (5-acetylamino-6-formylamino-3-methyluracil [AFMU] + 1-methyluric acid [1U] + 1-methylxanthine [1X] + 1,7-dimethyluric acid [17U] + 1,7-dimethylxanthine [17X])/137X) was also used as a measure of CYP1A2 activity.[33]

Pharmacokinetic and statistical analysis. The number of volunteers included was decided on by experience from previous studies. The low number of 5 EMs and 5 PMs at both doses of fluvoxamine was chosen to detect major but not minor inhibition effects. The concentration-versus-time data of parent drugs and metabolites were analyzed. The peak concentration (C_{max}) and the time to peak concentration (T_{max}) were obtained directly from the concentration-versus-time curves. The area under the concentration-versus-time curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity by use of the last measured plasma concentration and the elimination rate constant (λ_z), which was determined by log-linear regression analysis of the ter-

Table I. Pharmacokinetic parameters of fluvoxamine after a single dose and after multiple doses in extensive metabolizers (EMs) and poor metabolizers (PM) of debrisoquin (CYP2D6)

		Period 1			*Period 2*		*Period 3*	
	MR	C_{max} *(nmol/L)*	$t_{½}$ *(h)*	CL_{single} *(L/h · kg)*	CL_{ss}† *(L/h · kg)*	C_{ss} *(nmol/L)*	CL_{ss} *(L/h · kg)*	C_{ss} *(nmol/L)*
EMs								
1	0.69	61	15	1.30	1.2	36	—	—
2	0.57	39	15	2.00	2.1	32	1.90	11
4	1.04	40	17	1.50	1.3	39	—	—
5	1.08	35	17	1.80	1.3	33	2.30	7.3
8	0.60	45	16	1.50	1.4	44	1.80	11
12	2.20	142	24	0.43	—	—	0.51	52
13	0.67	45	19	0.92	—	—	0.65	28
Geometric mean	—	50	17	1.20	1.4	37	1.20	17
95% CI	—	44-61	15-20	0.76-2.0	1.1-1.9	31-43	0.51-2.9	6.1-45
PMs								
3	35	21	20	1.20	0.58	40	1.0	12
7	86	26	28	0.75	0.73	33	1.3	5.5
9	97	21	28	1.20	0.97	27	1.6	3.6
10	75	25	12	1.90	1.30	16	2.6	2.8
11	260	23	20	0.92	0.91	22	1.3	4.8
Geometric mean	—	23	21	1.10	0.86	26	1.5	5.0
95% CI	—	20-26	13-32	0.74-1.7	0.60-1.2*	17-41	0.97-2.3	2.6-9.8

For EMs: Period 1, single dose of 50 mg fluvoxamine; period 2, multiple doses of 25 mg × 2 of fluvoxamine; period 3, multiple doses of 10 mg × 2 of fluvoxamine. For PMs: period 1, single dose of 25 mg fluvoxamine; period 2, multiple doses of 25 mg × 1 fluvoxamine; period 3, multiple doses of 10 mg × 1 fluvoxamine. MR, Metabolic ratio of debrisoquin; C_{max}, maximal concentration; $t_{½}$, apparent half-life; CL_{single}, apparent oral clearance after a single dose; CL_{ss}, apparent oral clearance at steady state; C_{ss}, steady-state plasma concentration. Geometric mean and 95% confidence interval (95% CI) (antilog from standard error of the mean [SEM] of log values) are given.

*$P < .05$ (t test on log-transformed values for entire groups) when compared with extensive metabolizers. †By pairwise comparison, CL_{ss} was lower ($P < .05$) than CL_{single} in 10 subjects.

minal concentration-time points. The apparent half-life ($t_{½}$) was determined by the log-linear regression of the terminal points of the drug concentration-versus-time curve. The apparent oral plasma clearance (CL_{single}) was calculated as Dose/AUC. During steady state the oral clearance (CL_{ss}) was also calculated as Dose/AUC during the dosage interval of 12 hours for EMs and of 24 hours for PMs. The steady-state concentration (C_{ss}) of fluvoxamine was estimated as the mean of the trough values obtained on days 6 and 7.

For the statistical analysis the fluvoxamine C_{ss} and C_{max} values were divided by 2 in EMs because of the double dose given to EMs compared with PMs. The computer program Statistica, version 5.5 (StatSoft Inc, Tulsa, Okla) was used after logarithmic transformation of all pharmacokinetic parameters. Then 95% confidence intervals for the parameters were calculated from the antilog of the mean (n = 12, ± 2.20 × standard error of the mean [SEM]; n = 10, ± 2.26 × SEM) of log-transformed values. A t test on log-transformed values of caffeine and omeprazole parameters was used to compare the values between baseline and study periods 2 and 3, respectively. No comparison was made between period 2 and period 3 because of the change of 2 volunteers in period 3. For the pharmacokinetic parameters of fluvoxamine, the t test for independent groups (EMs compared with PMs) was used for statistical calculations. Spearman's rank correlation coefficient was used to compare the relationship between the AUCs of fluvoxamine and those of caffeine and omeprazole during fluvoxamine treatment, respectively. For this study, P values ≤.05 were regarded as significant.

RESULTS

Fluvoxamine kinetics. The fluvoxamine concentration-versus-time curves after single doses of fluvoxamine, 50 mg to EMs and 25 mg to PMs, are shown in Fig 2. EM subject No. 12 had very high concentrations of fluvoxamine compared with other subjects. The C_{max} of fluvoxamine was reached within 4 to 8 hours of dose administration. The geometric mean (per dose unit) of C_{max} was very similar in EMs (50 nmol/L after 50 mg) and PMs (23 nmol/L after 25 mg) (Table I). Also $t_{½}$ and CL_{single} were similar in EMs and PMs (Table I). After single doses of fluvoxamine, multiple doses of the drug were given (period 2) during 7 days to EMs (25 mg ×

Table II. Caffeine pharmacokinetics after a single oral dose of 100 mg given before and during steady-state concentration of fluvoxamine

	Cmax (μmol/L)			*$t_{½}$ (h)*			*AUC(0-24 h) (μmol · h/L)*			*Urinary caffeine N-3-demethylation index*		
Period	*1*	*3*	*2*	*1*	*3*	*2*	*1*	*3*	*2*	*1*	*3*	*2*
	Fluvoxamine dose											
	0 mg	*10 mg × 2*	*25 mg × 2*	*0 mg*	*10 mg × 2*	*25 mg × 2*	*0 mg*	*10 mg × 2*	*25 mg × 2*	*0 mg*	*10 mg × 2*	*25 mg × 2*
EMs												
1	5.8		18	7.5		28	54		317	59		12
2	12	13	19	8.5	10	31	139	202	340	52	30	8.3
4	6.8		26	3.2		16	34		404	491		32
5	6.2	5.9	8.4	4.9	5.6	11	43	66	122	101	78	12
8	8.6	15	40	5.5	8.5	28	94	192	719	84	33	14
12	12	40		4.2	32		103	700		153	27	
13	9.2	12		5.0	16		83	187		119	29	
	Fluvoxamine dose											
	0 mg	*10 mg × 1*	*25 mg × 1*	*0 mg*	*10 mg × 1*	*25 mg × 1*	*0 mg*	*10 mg × 1*	*25 mg × 1*	*0 mg*	*10 mg × 1*	*25 mg × 1*
PMs												
3	7.2	9.4	21	5.5	6.9	32	55	120	382	170	28	11
7	6.0	7.7	16	4.1	6.0	21	32	97	288	595	323	176
9	9.9	7.7	25	6.9	4.8	13	125	57	414	80	76	29
10	6.3	8.2	15	2.8	4.9	8.8	35	53	194	297	101	6.7
11	8.5	11	18	5.8	6.8	15	75	139	300	35	68	14
EMs + PMs												
Geometric mean	8.0	11	19	5.1	8.4	19	64	132	316	128	56	17.6
95% CI	6.7-9.4	7.6-16*	14-26***	4.1-6.3	5.5-13*	13-26***	46-89	76-229*	226-444***	73-224	31-99*	9.0-35***

The daily dose of fluvoxamine was 10 and 25 mg×2 to extensive metabolizers, 10 and 25 mg×1 to poor metabolizers of debrisoquine. Geometric mean and 95% confidence interval (antilog from SEM of log value is given. Cmax, Maximal concentration; t1/2, apparent half life; AUC(o-24h), area under the plasma concentration-time curve from time zero to 24 hours. Urinary *N*-3-demethylation index: (5-acetylamino-6-formylamino-3-methyluracil [AFMU] + 1-methyluric acid [1U] + 1-methylxanthine [1X] + 1,7-dimethyluric acid [17U] + 1,7-dimethylxanthine [17X])/caffeine [137X])in 24-hour urine collection.

*$P < .05$; ***$P < .001$ (paired *t* test on log-transformed values) when compared with value before fluvoxamine coadministration with 10 subjects in each group.

2) and PMs (25 mg × 1). The dose-corrected C_{ss} was not significantly different in EMs and PMs, but CL_{ss} was lower in PMs (geometric mean, 0.86 L/h per kilogram) compared with EMs (1.4 L/h per kilogram) ($P < .05$) (Table I). For the entire group (n = 10) receiving 25 or 50 mg of fluvoxamine, the CL_{ss} was lower (geometric mean, 1.1 L/h per kilogram) than the CL_{single} (1.3 L/h per kilogram) ($P < .05$).

During period 3 a lower dose of fluvoxamine was given for 7 days to EMs (10 mg × 2, daily) and PMs (10 mg × 1, daily). Only 3 of the 5 EMs, who had received the higher dose, could participate and 2 new EMs were, therefore, recruited. There were no significant differences in CL_{ss} or C_{ss} between EMs and PMs after this lower fluvoxamine dose (Table I). One of the new EMs, subject No. 12, had a very low CL after both the single dose (0.43 L/h per kilogram) and multiple dosing (0.51 L/hr per kilogram) (Table I).

The effect of fluvoxamine on caffeine pharmacokinetics and CYP1A2 activity. The pharmacokinetic parameters of caffeine in plasma and urine after a single oral dose of 100 mg before and during fluvoxamine are shown in Table II. The C_{max}, $t_{½}$, and AUC at 24 hours [AUC(0-24 h)] of caffeine increased markedly during administration of 25 mg × 1 or × 2 fluvoxamine daily ($P < .001$) compared with baseline (ie, without fluvoxamine treatment). A less pronounced, although significant ($P < .05$) effect on all three caffeine kinetic parameters was also shown after the lower 10 mg × 1 or × 2 dose of fluvoxamine. After the 10 mg × 1 or × 2 and 25 mg × 1 or × 2

Table III. Effect of steady-state concentration of fluvoxamine on AUC(0-8 h) of omeprazole and on 5-hydroxyomeprazole/omeprazole and omeprazole sulfone/omeprazole AUC(0-8 h) ratios

	AUC(0-8 h) of omeprazole (nmol · h/L)			*5-Hydroxyomeprazole/omeprazole AUC(0-8 h) ratio*			*Sulfone/omeprazole AUC (0-8 h) ratio*		
Period	*1*	*3*	*2*	*1*	*3*	*2*	*1*	*3*	*2*
	Fluvoxamine dose								
	0 mg	*10 mg × 2*	*25 mg × 2*	*0 mg*	*10 mg × 2*	*25 mg × 2*	*0 mg*	*10 mg × 2*	*25 mg × 2*
EMs									
1	751		4,159	1.5		0.33	0.93		0.43
2	1,515	3,449	5,767	0.78	0.41	0.24	0.60	0.24	0.58
4	540		4,457	1.8		0.33	0.61		0.46
5	1,016	3,034	4,391	1.1	0.45	0.32	1.0	0.48	0.53
8	1,051	2,792	5,631	2.0	0.73	0.44	0.51	0.45	0.55
12	5,375	15,443		0.38	0.14		0.50	0.36	
13	2,236	5,229		0.61	0.32		0.40	0.33	
	Fluvoxamine dose								
	0 mg	*10 mg × 1*	*25 mg × 1*	*0 mg*	*10 mg × 1*	*25 mg × 1*	*0 mg*	*10 mg × 1*	*25 mg × 1*
PMs									
3	1,672	2,831	7,899	1.2	0.50	0.33	0.43	0.28	0.26
7	967	3,016	5,435	1.4	0.55	0.35	0.68	0.58	0.41
9	404	775	3,552	2.6	1.5	0.55	0.56	0.63	0.34
10	589	1,444	2,775	2.1	0.87	0.53	0.55	0.43	0.57
11	561	1,666	3,037	2.6	0.98	0.65	0.44	0.55	0.42
EMs + PMs									
Geometric mean	1,045	2,867	4,499	1.3	0.54	0.39	0.58	0.41	0.44
95% CI	659-1,657	1,622-5,067***	3,582-5,650***	0.90-1.9	0.34-0.87***	0.31-0.49***	0.48-0.70	0.33-0.52*	0.37-0.53**

The fluvoxamine dose was 10 and 25 mg × 2 to EMs and 10 and 20 mg × 1 to PMs of debrisoquin. Geometric mean and 95% CI (antilog from SEM of log value is given). AUC(0-8h), area under the plasma concentration-time curve from time zero to 8 hours.

*$P < .05$; **$P < .01$;***$P < .001$ (paired *t* test on log-transformed values) when compared with value before fluvoxamine coadministration with 10 subjects in each group.

doses of fluvoxamine, the geometric mean values of caffeine AUC(0-24 h) increased about 2- and 5-fold, respectively. The C_{max} increased 40% during 10 mg × 1 or × 2 and 141% during 25 mg × 1 or × 2 fluvoxamine coadministration compared with baseline. The $t_{½}$ increased in a similar way. There was a strong correlation between the AUC(0-24 h) of caffeine and the AUC(0-24 h) of fluvoxamine ($r_s = 0.82$; $P < .001$; n = 32) (Fig 3, *A*).

The geometric mean values of the urinary caffeine *N*-3-demethylation index decreased by 57% and 86% during the multiple dosing with 10 mg × 1 or × 2 and 25 mg × 1 or × 2 of fluvoxamine, respectively. This effect of fluvoxamine on CYP1A2, measured as the urinary ratio, is similar to the effect on the plasma AUC of caffeine. The urinary *N*-3-demethylation index was correlated with the plasma AUC(0-24 h) of caffeine ($r_s = 0.74$; $P < .001$; n = 32).

In subject No. 12, a remarkable increase of the caffeine pharmacokinetic parameters was observed compared with other subjects during the 10 mg × 1 or × 2 daily dose of fluvoxamine [a more than 3-fold increase of C_{max}, a prolonged $t_{½}$ from 4 to 32 hours, and a nearly 7-fold increase of AUC(0-24)]. However, compared with baseline, the changes in C_{max}, $t_{½}$, and AUC(0-24 h) were significant ($P < .05$) during the 10 mg × 1 or × 2 daily fluvoxamine doses even when subject No. 12 was excluded from the calculations.

The effect of fluvoxamine on omeprazole disposition and CYP2C19 and CYP3A4 activities. The AUC(0-8 h) of omeprazole and the 5-hydroxyomeprazole/omeprazole and sulfone/omeprazole AUC ratios after single oral doses of 20 mg omeprazole before and after treatment with fluvoxamine are shown in Table III. The geometric means of omepra-

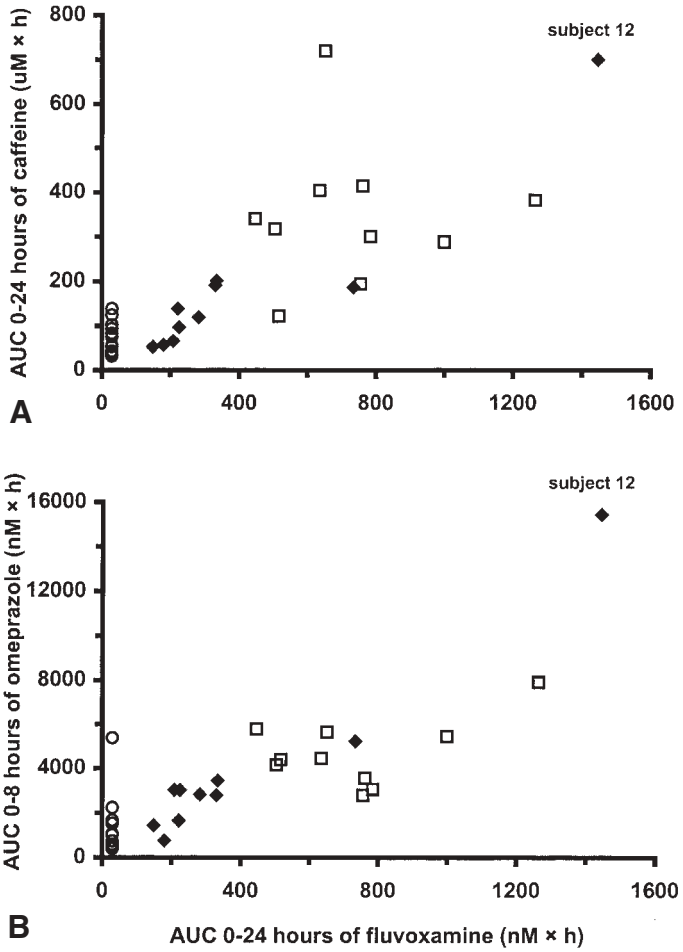

Fig 3. A, Relationship between caffeine area under the concentration-versus-time curve [AUC(0-24 h)] and fluvoxamine AUC(0-24 h) after a 100-mg caffeine dose in healthy volunteers before (*open circles*, n = 12) and after a low dose (10 mg × 1 to PMs, 10 mg × 2 to EMs; *solid diamonds*; n = 10) and a high dose (25 mg × 1 to PMs and 25 mg × 2 to EMs; *open squares*; n = 10) of fluvoxamine (r_s = 0.82; P < .001; n = 32). EMs were given fluvoxamine every 12 hours, and the AUC(0-24 h) in this case is, therefore, twice the AUC(0-12 h). **B,** Omeprazole AUC(0-8 h) after a 20-mg dose versus AUC(0-24 h) of fluvoxamine (r_s = 0.79; P < .001; n = 32), before and after a low or high dose of fluvoxamine, as described.

zole AUC(0-8 h) increased with 174% (P < .001) with 10 mg × 1 or × 2 and 330% (P < .001) with 25 mg × 1 or × 2 of fluvoxamine. The AUC(0-8 h) ratios of the metabolites over the mother compound have previously been described as indices of the CYP2C19 (5-hydroxyomeprazole/ omeprazole) and CYP3A4 (sulfone/omeprazole) activities.[35,46] The geometric means of the AUC(0-8 h) ratio 5-hydroxyomeprazole/omeprazole decreased by 59% (P < .001) and 70% (P < .001) during the fluvoxamine doses 10 mg × 1 or × 2 and 25 mg × 1 or × 2, respectively. Similarly, the AUC(0-8 h) ratio sulfone/omeprazole decreased by 29% (P < .05) and 24% (P < .01). Thus the marked increase in omeprazole plasma concentration resulted in a considerable decrease especially of CYP2C19 but also of CYP3A4 indices. Both the AUC(0-8 h) of omeprazole (r_s = 0.79; P < .001; n = 32) (Fig 3) and the AUC(0-8 h) ratio 5-hydroxyomeprazole/omeprazole (r_s = –0.75; P < .001; n = 32) correlated strongly with the AUC(0-24 h) of fluvoxamine at steady state. The ratio sulfone/omeprazole was less but still significantly correlated with fluvoxamine AUC(0-24) (r_s = –0.52; P < .05; n = 32).

Subject No. 12, who had the highest fluvoxamine AUC, also had the highest omeprazole AUC after daily intake of 10 mg × 2 fluvoxamine (Fig 3).

Side effects. None of the subjects stopped taking fluvoxamine as a result of side effects. However, all of the subjects except one reported several side effects, although they were moderate in severity. Side effects were rather frequent both after the single dose and during the first 2 days of multiple dosing. No difference in the side effect profile was seen between EMs and PMs or the low dose and the high dose of fluvoxamine. The side effects reported were insomnia (3 subjects), diarrhea (3 subjects), dizziness (4 subjects), headache (5 subjects), dry mouth (4 subjects), nausea (3 subjects), stomach pain (4 subjects), tiredness (3 subjects) and loss of taste (2 subjects). No side effects were reported after intake of caffeine or omeprazole.

DISCUSSION

The major finding in this study was that fluvoxamine even in low doses (10 mg × 1 or × 2 per day) has a significant (40%-50%) and about equal inhibitory effect on the metabolism of the CYP1A2 and CYP2C19 probe drugs. At the higher daily fluvoxamine dose (50 mg to EMs, 25 mg to PMs) a more than 75% inhibition of both enzymes was seen. Thus a dose-dependent inhibition of both enzymes was found. The low doses of fluvoxamine used in this study have not previously been shown to inhibit these enzymes in vivo.

After our study was finalized, in vitro data describing a similar and potent inhibition of CYP1A2 and CYP2C19 (K_i, 41 and 87 nmol/L, respectively) by fluvoxamine were published.[43] These in vitro data are in agreement with the findings in our study. However, the amount of the different CYPs in the liver tissue varies among individuals. Therefore extrapolation of in vitro data to the in vivo situation, concerning the quantitative increase in plasma concentration of a drug when fluvoxamine is used concomitantly, is likely to be associated with uncertainty. In addition, the inhibitory effects of metabolites are not investigated in vitro.

Fluvoxamine may cause clinically important interactions not only with drugs metabolized by CYP1A2 but also with those metabolized by CYP2C19. This is supported by previous findings of interactions with drugs such as imipramine,[11] clomipramine, amitriptyline,[7] thioridazine,[47] and diazepam.[48] The inhibition of the *N*-demethylation of these drugs by fluvoxamine is probably due to the inhibition of both CYP1A2[49] and CYP2C19. The formation of 5-hydroxyomeprazole from omeprazole is almost exclusively catalyzed by CYP2C19.[36] Our results clearly show that low doses of fluvoxamine cannot be used to selectively inhibit the CYP1A2 enzyme.

Omeprazole is, to a minor extent, metabolized to a sulfone, and this reaction is mainly catalyzed by CYP3A4.[37] In PMs of *S*-mephenytoin, this is the predominant metabolic pathway.[37,50] Limited evidence has suggested that fluvoxamine has an inhibitory effect on CYP3A4, measured as increased plasma concentrations of alprazolam during fluvoxamine coadministration.[38] Thus a decreased formation of the sulfone could be expected in combination with fluvoxamine. However, in our study the concentrations of the sulfone increased almost to the same extent as those of omeprazole. Although the AUC ratio sulfone/omeprazole decreased significantly after both the low and higher fluvoxamine doses (Table III), the effect on this CYP3A4 index was smaller than that on the CYP1A2 and CYP2C19 indices. The possibility of a CYP3A4 inhibition by fluvoxamine needs to be studied with normal clinical doses (100 to 300 mg daily) of fluvoxamine.

Our hypothesis was that higher plasma concentrations of fluvoxamine develop in PMs of debrisoquin than in EMs given the same dose. Therefore EMs were given double the dose compared with that given to PMs to obtain similar plasma levels. However, we found no difference in fluvoxamine clearance between EMs and PMs after single doses. We found only a significantly lower clearance of fluvoxamine in PMs compared with EMs during the higher steady-state fluvoxamine dose and not at the lower dose (Table I). Even without EM subject No. 12, who had a low fluvoxamine clearance after both the single dose and the low multiple doses, there was no clear CYP2D6-dependent kinetics of fluvoxamine in this study. Factors other than CYP2D6 seem to be of more importance for the disposition of fluvoxamine.

Within the therapeutic dose interval (ie, 100-300 mg daily), fluvoxamine exhibits nonlinear kinetics.[19,20] Even at the low doses of fluvoxamine used in this study, there was a slightly but significantly lower clearance of the drug after the 25 mg × 1 or × 2 multiple doses than after the single doses.

EM subject No. 12 was found to have very high plasma concentrations (Fig 2) and a low clearance of fluvoxamine after both single and multiple dosing (Table I). This subject had a debrisoquin metabolic ratio of 2.2 and the genotype *CYP2D6*1/*5*. She is, thus, a heterozygous EM of debrisoquin. A defective CYP2D6 cannot, therefore, explain the low clearance of fluvoxamine in this subject. This also does not seem to be due to a low CYP1A2 capacity, because the urinary caffeine *N*-3-demethylation index and the caffeine plasma concentrations at baseline were about the same as in the other subjects (Table II). However, after coadministration of 10 mg × 2 fluvoxamine, the AUC(0-24 h) for caffeine increased almost 7-fold in

this subject compared with 2-fold or less in the other subjects (Table II and Fig 3). The omeprazole AUC(0-8 h) increased almost 3-fold, which was about the same as for the other subjects. On the other hand, this subject started with baseline plasma concentrations of omeprazole that were 2.5 to 10 times higher than in the other subjects. She had a mephenytoin *S/R* ratio of 0.71 (ie, she was an EM but with a metabolic ratio very close to that of PMs of CYP2C19 [ratio about 1]). However, she had the genotype *CYP2C19*1/*1*, confirming that she was an EM. The high plasma concentrations of fluvoxamine and omeprazole suggest that this subject may have had a higher bioavailability of these drugs than the other subjects had. The reason for this finding can only be speculated. If fluvoxamine and omeprazole were substrates for P-glycoprotein or another transporter of drugs back to the intestinal lumen after absorption, the presence of a defect transport protein would result in a higher absorption of these drugs. It is interesting that a polymorphism in the *MDR 1* gene coding for P-glycoprotein has recently been reported.[51] A low affinity for omeprazole to P-glycoprotein has recently been demonstrated.[52] However, the affinity of fluvoxamine to P-glycoprotein is not known. We suggest that a possible explanation for the high plasma concentrations of fluvoxamine in subject No. 12 might be a defective transporter protein (for example, P-glycoprotein). This finding is under further investigation.

We have previously evaluated a single oral dose of caffeine as a probe for CYP1A2 activity.[33] It was concluded that the caffeine plasma clearance, the 4-hour paraxanthine/caffeine plasma ratio, and the ratio of *N*-3-demethylated caffeine metabolites divided by caffeine in a 24-hour urine collection all serve as criterion standards for measuring CYP1A2 activity. In this study the time for blood sampling of caffeine was the same in all 3 periods (24 hours). Because the low doses of fluvoxamine used in our study caused a pronounced inhibition of caffeine disposition, measured as an increase of plasma C_{max}, $t_{½}$, and AUC, we were not able to measure the caffeine AUC from time zero to infinity when CYP1A2 was inhibited by fluvoxamine, because of the very long $t_{½}$ of caffeine. On the other hand, the AUC(0-24 h) of caffeine was strongly correlated with the urinary caffeine *N*-3-demethylation index, which is in accordance with our previous finding.[33]

The previous knowledge of a CYP2C19 inhibition by fluvoxamine at higher doses than we used in our study[42] convinced us to use a probe for this enzyme. The inhibition of CYP2C19 by fluvoxamine was clearly reflected by the increase in omeprazole AUC(0-8 h) and the decrease in AUC ratio of 5-hydroxyomeprazole/omeprazole.

In conclusion, we have shown that low doses of fluvoxamine potently inhibit both CYP1A2 and CYP2C19, whereas the inhibition of CYP3A4 is moderate. In clinical practice, important interaction risks exist when fluvoxamine is coadministered with other drugs metabolized by either CYP1A2 or CYP2C19 or both.

We thank E. Götharsson, RN, and J. Widén for their expert assistance.

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