Non-linear fluvoxamine disposition

Olav Spigset, Kerstin Granberg, Staffan Hägg, Emma Söderström & Rune Dahlqvist

Division of Clinical Pharmacology, Norrland University Hospital, Umeå, Sweden

Aims To study the pharmacokinetics of fluvoxamine when given in increasing doses to healthy volunteers.

Methods Ten healthy, non-smoking men were given maintenance treatment with fluvoxamine for 4 weeks. Eight subjects were CYP2D6 extensive metabolisers (EMs) and two were CYP2D6 poor metabolisers (PMs). As a measure of the CYP1A2 phenotype, the paraxanthine/caffeine ratio in saliva after intake of caffeine was studied. The fluvoxamine doses given were 25 mg day⁻¹ the first week, 50 mg day⁻¹ the second week, 100 mg day⁻¹ the third week and 200 mg day⁻¹ the fourth week, divided in two daily doses. On the seventh day every week, serum concentrations of fluvoxamine were followed for a dose interval of 12 h. After discontinuation of treatment, fluvoxamine concentrations were followed for 1 week.

Results For each of the three two-fold increases in given dose, the mean AUC increased 3.25-fold, 3.17-fold and 3.14-fold, respectively ($P < 0.0001$), indicating a decrease in oral clearance with increasing dose. The elimination half-life based upon the serum concentrations 12–48 h after discontinuation of fluvoxamine was 32.1 ± 11.0 h whereas the half-life based upon the concentrations 3–7 days after discontinuation was significantly shorter, 15.8 ± 4.2 h (means $\pm$ s.d.; $P < 0.001$). There were no significant correlations between the CYP1A2 phenotype and fluvoxamine AUCs at different doses ($r = -0.56$; $P = 0.095$ for the correlation between the paraxanthine/caffeine ratio in saliva and fluvoxamine AUC at a dose of 50 mg day⁻¹). The two CYP2D6 PMs had AUC values in the same range as the EMs.

Conclusions The present study conclusively demonstrates that fluvoxamine exhibits non-linear kinetics within the therapeutic dose interval. The reason for non-linearity is not Michaelis-Menten saturation kinetics of a single metabolic pathway, but rather a complex involvement of multiple parallel pathways.

Keywords: CYP1A2, CYP2D6, fluvoxamine, non-linear, disposition, pharmacokinetics, adverse drug reactions

Introduction

The selective serotonin reuptake inhibitor fluvoxamine is used in the treatment of depression and obsessive compulsive disorder, and is currently evaluated in the treatment of a number of other psychiatric diseases [1, 2]. Fluvoxamine is extensively metabolised in the liver [3], and the limited data available indicate that it is a high clearance drug [4]. There are some data to indicate that the isozymes CYP1A2 [5] and CYP2D6 [6], but not CYP2C19 [6], are important for its metabolism. Fluvoxamine is a potent inhibitor of CYP1A2 *in vitro* [7, 8] as well as *in vivo* [9–13]. Saturation kinetics have been demonstrated for other drugs metabolised by CYP1A2, such as theophylline and caffeine [14–16], and drug metabolism by the polymorphic isozyme CYP2D6 is also characterised by saturation kinetics [17].

There is evidence to suggest that fluvoxamine may exhibit non-linear kinetics. In a crossover study in six healthy volunteers [18], area under the concentration–time curve

(AUC) over a dose interval at steady-state (dose 50 mg $\times$ 2) was 30% higher than predicted from AUC from 0 to infinity after a single dose of 50 mg. Moreover, the terminal half-lives were 20–50% longer at steady state than in the same subjects after a single dose [18]. In a study of nine patients with depression, doubling the fluvoxamine dose from 100 to 200 mg day⁻¹ caused a 3.3-fold increase in the mean steady state plasma concentration [19]. On the other hand, no indications of non-linearity were found in the dose range 25–100 mg after single oral doses [20], and according to some unpublished data (cited in [21]), linearity has been demonstrated in the 100 to 300 mg day⁻¹ dose range in two small clinical studies. In a recent case report of fluvoxamine intoxication [22], in which serum concentrations of fluvoxamine were followed for 1 week, non-linearity was apparently present at serum levels over 150 ng ml⁻¹ (approximately 500 nmol l⁻¹). The half-life of the first part of the elimination phase was 38 h, which is longer than other reports in the literature, except among some patients with liver cirrhosis [23]. In contrast, the half-life of the terminal elimination phase was 19 h.

In order to study the non-linear kinetics of fluvoxamine

Correspondence: Dr Olav Spigset, Department of Clinical Pharmacology, Regional and University Hospital, N-7006 Trondheim, Norway.

more thoroughly and to elucidate the role of different enzymes involved, we performed a pharmacokinetic study in which fluvoxamine was given in increasing doses to healthy volunteers.

Methods

Subjects

After giving their informed consent, 10 non-smoking men took part in the investigation, which was approved by the Ethics Committee at Umeå University. Their age (mean $\pm$ s.d.) was 28.9 ± 5.2 years, and their body weight was 85.6 ± 7.6 kg. All subjects were healthy, as assessed by medical history, physical examination, and routine blood chemistry tests. They had been entirely drug-free for at least 2 weeks prior to study start. Drugs taken as needed during the study period included single doses of bromhexine, chlorzoxazone, codeine, dextropropoxyphene, ephedrine, ibuprofen and paracetamol. These drugs were never ingested less than 3 days before the study days.

Study protocol

Fluvoxamine (Fevarin; enteric-coated fluvoxamine maleate, Solvay Duphar B.V., Vesp, The Netherlands) was given to the subjects in increasing doses for a total of 4 weeks. The doses were 25 mg day^{-1} the first week, 50 mg day^{-1} the second week, 100 mg day^{-1} the third week, and 200 mg day^{-1} the fourth week. Half of the daily dose was ingested at 08.00 h and the other half at 20.00 h.

On the seventh day at each dose level, venous blood samples (10 ml) were drawn at 08.00 h, and 1, 2, 3, 4, 6, 8, 10, and 12 h later. Serum was separated within 30 min and stored frozen at -80°C until analysis. On these study days, the tablet intake at 08.00 h was followed by a standardized, light breakfast meal at 08.30 h, a standardized lunch at noon, and a standardized dinner at 17.00 h. Intake of alcohol and of food or beverages containing caffeine or other methylxanthines was not allowed on the study days and was otherwise registered daily throughout the study period. After discontinuation of fluvoxamine at the end of week 4, single blood samples were, in addition to the samples obtained during the first 12 h after tablet intake, also obtained after 24, 32 and 48 h, and thereafter once daily except Sundays for a total period of 1 week. Throughout the study, the subjects daily registered possible adverse effects of fluvoxamine by open reporting on a registration sheet.

CYP2D6 phenotyping

The CYP2D6 phenotype was determined after intake of 50 mg dextromethorphan hydrobromide (Tussidyl mixture, 2 mg ml^{-1} ; Tika, Lund, Sweden) and collection of urine for 10 h. Dextromethorphan and its O-demethylated metabolite dextrorphan were analysed by a capillary gas chromatography method described in detail elsewhere [6]. Using this method, dextromethorphan/dextrorphan ratios >0.9 defined the poor metabolisers, whereas ratios <0.9 defined the extensive metabolisers. The subjects were chosen to include eight CYP2D6 extensive metabolisers (EMs) and

two CYP2D6 poor metabolisers (PMs). The EMs had metabolic ratios ranging from 0.03 to 0.47, and the PMs had metabolic ratios of 1.9 and 48, respectively.

CYP2C19 phenotyping

The CYP2C19 phenotype was determined after intake of 100 mg racemic mephenytoin (Mesantoin; Sandoz, Basel, Switzerland) and collection of urine for 10 h [6]. The analytical method used is described in detail elsewhere [24]. Using this method, mephenytoin S/R enantiomeric ratios >0.8 defined the poor metabolisers, whereas ratios <0.8 defined the extensive metabolisers. All subjects were CYP2C19 extensive metabolisers with metabolic ratios ranging from 0.02 to 0.18.

CYP1A2 phenotyping

As a measure of CYP1A2 metabolic capacity, the paraxanthine/caffeine ratio in saliva was studied [25]. After methylxanthine abstinence for at least 30 h, 200 mg caffeine (2 tablets of 100 mg Koffein ACO; ACO AB, Helsingborg, Sweden) was ingested. Seven hours later, 1.5 ml saliva was collected into polyethylene tubes by the spit method without chemical stimulation. All samples were stored at -20°C until analysis.

Concentrations of caffeine and paraxanthine were analysed by a high performance liquid chromatography (h.p.l.c.) method developed in our laboratory. After thawing, the saliva samples were centrifuged at $11\,000 g$ for 2 min. Solid-phase extraction cartridges (Isolute MF C18; International Sorbent Technology, Mid Glamorgan, UK) were prepared by prewashing with $2 \times 1 \text{ ml}$ methanol and $2 \times 1 \text{ ml}$ water. $240 \mu\text{l}$ saliva, $60 \mu\text{l}$ (14.39 ng) of the internal standard β -hydroxyethyltheophylline, and $900 \mu\text{l}$ water was gently mixed, and 1 ml of the mixture was applied to the column. Thereafter, the column was washed with $2 \times 1 \text{ ml}$ water and $350 \mu\text{l}$ acetone and the methylxanthines were eluted with $800 \mu\text{l}$ acetone. After the eluate was evaporated to dryness under nitrogen and redissolved in $100 \mu\text{l}$ of the mobile phase by ultrasound, $40 \mu\text{l}$ were injected onto the chromatograph. The mobile phase consisted of 3 mM sodium acetate ($\text{pH } 4.0$) with 1.4% acetonitrile, 1% methanol, and 1.6% tetrahydrofuran stabilised with 0.025% butylated hydroxytoluene. The separation was performed on a Nucleosil ODS $5 \mu\text{m}$ 25 cm column (Jones Chromatography, Mid Glamorgan, UK) with a flow of 1.2 ml min^{-1} . The ultraviolet detector was set at a wavelength of 273 nm . Mean ($\pm$ s.d.) recoveries after solid-phase extraction were 97.6% ($\pm 3.2\%$) for caffeine, 99.8% ($\pm 4.5\%$) for paraxanthine, and 94.8% ($\pm 2.4\%$) for β -hydroxyethyltheophylline. At a concentration of $10 \mu\text{mol l}^{-1}$, the intraassay coefficients of variation were 2.7% for paraxanthine and 1.8% for caffeine, and the interassay coefficients of variation were 2.9% and 4.0% , respectively. The limit of quantification was $0.5 \mu\text{mol l}^{-1}$, and the method was linear at least up to $250 \mu\text{mol l}^{-1}$. The salivary concentrations of caffeine and paraxanthine in the volunteers ranged from 3.4 to $9.6 \mu\text{mol l}^{-1}$ and from 3.3 to $4.5 \mu\text{mol l}^{-1}$, respectively, and the paraxanthine/caffeine ratios ranged from 0.36 to

1.14. Unfortunately, the ratio from one CYP2D6 PM was not available for administrative reasons.

Fluvoxamine analysis

The serum concentrations of fluvoxamine were determined by a h.p.l.c. method described in detail elsewhere [5]. In brief, to 2 ml serum were added 5 ml 0.3 M Na_3PO_4 and 400 μl di-isopropylether. After mixing and centrifuging, the organic layer was separated on a straight phase 150×4.6 mm Apex Silica 3 μm column and analysed with the ultraviolet detector set at a wavelength of 254 nm. The limit of quantification was 0.5 nmol l^{-1} and the method was linear at least up to 3000 nmol l^{-1} .

Pharmacokinetic and statistical analyses

Trough serum concentrations of fluvoxamine at steady state (C_0), peak serum concentrations of fluvoxamine at steady state (C_{max}) and time of peak concentrations (t_{max}) were derived directly from the measured values. Other pharmacokinetic parameters were calculated by use of the pharmacokinetic program package Siphar/Win, version 1.13 (SIMED S.A., Creteil, France). Areas under the serum concentration-time curves during the dose intervals of 12 h at steady state (AUC) were calculated by use of the linear trapezoidal rule. Average serum concentrations at steady-state (C_{av}) were calculated as $\text{AUC}/12 \text{ h}$. Oral clearance (CL/F , in which F is the oral bioavailability) was calculated as $\text{Dose (half of the daily dose)}/\text{AUC}$. The parameter estimates describing the linear slopes of the log-concentration of fluvoxamine were calculated by means of the peeling procedure in the program package. For each subject, two slopes were calculated: λ_{12-48} , which is the slope represented by the serum concentrations 12, 24, 32 and 48 h after discontinuation of fluvoxamine, and λ_z , which is the slope represented by the four last measurable serum concentrations. The corresponding half-lives ($t_{1/2,12-48}$ and $t_{1/2,z}$) were calculated as $\ln 2/\lambda_{12-48}$, and $\ln 2/\lambda_z$, respectively. In addition, the presence of non-linear kinetics was evaluated by plotting the daily dose/ C_{av} ratio against daily dose (Eadie-Hofstee plot with interchanged axes).

For comparisons of pharmacokinetic parameters at different dose levels, two-way analysis of variance was used. For comparisons of elimination half-lives, paired Student's t -test was used. For the study of correlations between variables, Pearson's correlation test was used. Metabolic ratios were log-transformed prior to the inclusion in the analyses. All calculations were carried out by the SYSTAT program package, version 5.2.1. (Systat Inc., Evanston, IL, USA). P values of less than 0.05 were regarded as statistically significant.

Results

The pharmacokinetic parameters for the four different maintenance doses of fluvoxamine are presented in Table 1, and the increases in fluvoxamine average steady-state concentrations with increasing doses are illustrated in Figure 1. There was a consistent and disproportionate increase in fluvoxamine AUC values throughout the dose

Figure 1 Plot of fluvoxamine dose against average steady-state serum concentration in eight CYP2D6 extensive metabolisers (whole lines) and two CYP2D6 poor metabolisers (dotted lines). Identical symbols in Figures 1–3 represent the same subject.

range studied ($P < 0.0001$). Relative to the AUC/dose ratio at 25 mg day^{-1} , the mean increase was 58% at 50 mg day^{-1} , 153% at 100 mg day^{-1} , and 299% at 200 mg day^{-1} . Mean AUC ratios for the doses 50 mg vs 25 mg , 100 mg vs 50 mg , and 200 mg vs 100 mg were fairly constant, 3.25, 3.17 and 3.14, respectively. All subjects showed disproportionate increases in C_0 and C_{max} , and a marked decrease in CL/F with increasing doses ($P < 0.0001$ for all parameters). There were no changes in t_{max} with increasing doses. Mean C_{max}/C_0 ratios decreased significantly with increasing dose and were 1.96 ± 0.78 at a dose of 25 mg day^{-1} , 1.62 ± 0.32 at a dose of 50 mg day^{-1} , 1.51 ± 0.21 at a dose of 100 mg day^{-1} , and 1.48 ± 0.41 at a dose of 200 mg day^{-1} ($P = 0.008$).

Individual elimination rates after discontinuation of fluvoxamine are illustrated in Figure 2. Mean $t_{1/2,12-48}$ was $32.1 \pm 11.1 \text{ h}$ (range 11.5–45.5 h) whereas mean $t_{1/2,z}$ was $15.8 \pm 4.2 \text{ h}$ (range 7.9–19.4 h) ($P < 0.001$). There was a considerable interindividual variation in the average steady-state concentrations (Table 1, Figure 1). For example, at a dose of 100 mg day^{-1} , a 6.8-fold variation in average steady-state serum concentrations was encountered. Moreover, the subject with the lowest serum concentrations had an average steady-state concentration at a dose of 200 mg day^{-1} that the subject with the highest serum concentrations would be expected to have at a dose of approximately 75 mg day^{-1} .

There were no correlations between age, body weight, or CYP2C19 metabolic ratio and AUC at different dose levels. There was a non-significant, negative correlation between paraxanthine/caffeine ratio in saliva and fluvoxamine AUC ($r = -0.48$ at 25 mg day^{-1} ; $r = -0.56$ ($P = 0.095$) at 50 mg day^{-1} , $r = -0.33$ at 100 mg day^{-1} ; $r = -0.13$ at 200 mg day^{-1}). The two CYP2D6 PMs had fluvoxamine concentrations (Figure 1) and AUC values (Table 2) within the range of the eight CYP2D6 EMs. In both the EMs and the PMs, the plots of daily dose/ C_{av} against daily dose revealed downward convex curves of essentially the same shape (Figure 3).

At the doses 25 and 50 mg day^{-1} , fluvoxamine was well tolerated. During the 2 weeks at these doses, one subject

Table 1 Pharmacokinetic parameters for fluvoxamine at steady-state in 10 healthy volunteers given fluvoxamine in increasing doses for 4 weeks.

Week	Dose (mg day ⁻¹)	C ₀ (nmol l ⁻¹) Mean ± s.d. (range)	C _{max} (nmol l ⁻¹) Mean ± s.d. (range)	t _{max} (h) Median (range)	AUC (nmol l ⁻¹ h) Mean ± s.d. (range)	CL/F (ml min ⁻¹) Mean ± s.d. (range)	AUC/dose (nmol l ⁻¹ h mg ⁻¹)★ Mean ± s.d. (range)
1	12.5 × 2	14.7 ± 7.1 (2.7–26)	25.1 ± 9.4 (9.6–41)	3.5 (3–6)	236 ± 95 (71–394)	3464 ± 2185 (1689–9372)	18.9 ± 7.6 (5.7–31.5)
2	25 × 2	50.1 ± 19.8 (15–86)	76.3 ± 22.1 (35–117)	2.5 (2–6)	745 ± 258 (264–1216)	2088 ± 1107 (1094–5041)	29.8 ± 10.3 (10.6–46.8)
3	50 × 2	168 ± 73.6 (36–264)	244 ± 97.9 (70–423)	2.5 (2–4)	2391 ± 949 (602–4072)	1441 ± 1089 (654–4421)	47.8 ± 19.0 (12.0–81.4)
4	100 × 2	593 ± 297 (103–974)	738 ± 314 (261–1303)	3.5 (1–8)	7545 ± 3239 (2069–13 187)	925 ± 649 (404–2573)	75.5 ± 32.4 (20.7–132)

★ratio between the 12 h AUC and the 12 h dose (=half of the daily dose).

C₀=trough serum concentration. C_{max}=peak serum concentration. t_{max}=time of peak serum concentration. AUC=area under the serum concentration–time curves during the dose interval of 12 h. CL/F=oral clearance. s.d.=standard deviation.

Figure 2 Elimination rates of fluvoxamine in eight CYP2D6 extensive metabolisers (whole lines) and two CYP2D6 poor metabolisers (dotted lines) after discontinuation of fluvoxamine. The subjects had been treated with fluvoxamine 200 mg day⁻¹, and steady-state conditions were achieved in all subjects. The abscissa represents the time after the last dose of fluvoxamine was ingested. Identical symbols in Figures 1–3 represent the same subject.

Figure 3 Plot of fluvoxamine daily dose/average steady-state serum concentration ratio against daily dose in eight CYP2D6 extensive metabolisers (whole lines) and two CYP2D6 poor metabolisers (dotted lines). Identical symbols in Figures 1–3 represent the same subject.

Week	Dose (mg day ⁻¹)	Extensive metabolisers Mean ± s.d. (range)	Poor metabolisers Mean (range)
1	25	247 ± 104 (71–394)	194 (183–204)
2	50	775 ± 282 (264–1216)	616 (572–659)
3	100	2472 ± 1053 (602–4072)	2068 (1605–2530)
4	200	7974 ± 3401 (2069–13 187)	5838 (3766–7909)

s.d.=standard deviation.

had transitory light headache, one had intermittent diarrhoea, and two experienced transient nausea. At a dose of 100 mg day⁻¹, five of the volunteers experienced more long-lasting adverse drug reactions, including nausea and drowsiness (two subjects), nausea, headache, and excessive yawning. At a dose of 200 mg day⁻¹, all but one subject

reported adverse drug reactions. These were drowsiness (*n* = 7), nervousness/restlessness (*n* = 6), nausea, particularly after sports and training (*n* = 4), excessive yawning (*n* = 4), headache (*n* = 3), insomnia (*n* = 3), tremor (*n* = 2), dyspepsia (*n* = 1), decreased libido (*n* = 1), paraesthesias (*n* = 1), diarrhoea (*n* = 1) and dry mouth (*n* = 1). No subjects interrupted

Table 2 AUC (nmol l⁻¹ h) for CYP2D6 extensive metabolisers (*n* = 8) and CYP2D6 poor metabolisers (*n* = 2) given fluvoxamine in increasing doses for 4 weeks.

the treatment due to adverse effects. There was a close to significant positive correlation between the number of suspected adverse drug reactions reported during week 4 and the trough fluvoxamine serum concentration at the end of the same week (Figure 4) ($r=0.62$; $P=0.057$).

Discussion

The present study clearly demonstrates that fluvoxamine AUC disproportionately increases with increasing doses within the clinically used dose range. The evidence of non-linear kinetics of fluvoxamine confirms the results from some earlier studies [18, 19, 22].

For practical reasons as well as for safety reasons, the order of the different maintenance doses of fluvoxamine were not randomised, but were given in order of increasing dose. In the statistical analysis, a possible effect of the order of treatment can therefore not be separated from that due to the different doses. However, the shape of the concentration-time curves after discontinuation of fluvoxamine clearly supports that our findings are dose-dependent rather than time-dependent.

The design of the study does not allow us to state with certainty that steady-state conditions have been achieved at all dose levels. Based on the elimination half-lives reported in the literature [3–6, 18, 20, 21, 26], it seems reasonable that steady-state conditions have been achieved at doses of 25 and 50 mg day⁻¹. At doses of 100 and 200 mg day⁻¹, mean increases in concentrations from 0 to 12 h post-dose day 7 were 2.6% and 0.1%, respectively, indicating that conditions close to steady-state have been achieved. Moreover, initial half-lives after discontinuation of fluvoxamine (Figure 2) can roughly be estimated to be less than 50 h in most cases, although it cannot be excluded that a few subjects might have initial half-lives up to 100 h. Nevertheless, if steady-state conditions have not been achieved at the highest dose levels, the real differences will, in fact, be larger than found in the current study.

In the only study where fluvoxamine has been given intravenously [4], mean oral bioavailability was 53%. Based on the mean AUC value in that study, clearance can be

estimated to be approximately 2100 ml min⁻¹ after a single intravenous dose of 30 mg. Thus, fluvoxamine is a high clearance drug, at least at low doses. The high clearance values compared with liver blood flow are probably mainly caused by the fact that the concentration of fluvoxamine is 50–70% higher in erythrocytes than in serum (unpublished observations from our laboratory), although the possibility of extrahepatic metabolism cannot be excluded. As shown in the present study, oral clearance will clearly decrease with increasing fluvoxamine dosage and serum concentrations. Moreover, in subjects lacking functional CYP2D6 and having a low metabolic capacity of other major enzymes involved in fluvoxamine metabolism, fluvoxamine behaves as a low-clearance rather than a high-clearance drug [26].

In most other studies, mean elimination half-lives of fluvoxamine in healthy, young volunteers have been 15–20 h after single oral doses of 25–100 mg [3, 18, 20, 21], although several recent studies have reported mean half-lives of 10–14 h [4–6, 26]. The terminal elimination half-lives ($t_{1/2,z}$) seen in the present study correspond well with these values. The half-lives based on the serum concentrations 12–48 h after the last dose ($t_{1/2,12-48}$) are longer than ever reported earlier, except among patients with liver cirrhosis [23] and after fluvoxamine overdose [22]. Moreover, as seen in Figure 2, these half-lives most probably are an underestimation of the real initial half-lives.

Plots of daily dose/ C_{av} ratio against daily dose should yield a horizontal line (slope=0) if the elimination pathway involved exhibits linear kinetics at the concentrations studied, and would have a negative slope if the pathway is saturable at the concentrations studied. A curvilinear plot with a downwards convex slope (negative slope decreasing), as here, implies the coexistence of multiple parallel pathways. In both the eight CYP2D6 EMs and the two CYP2D6 PMs, the plots revealed downward convex curves. Thus, our results indicate that several parallel metabolic pathways exist in CYP2D6 PMs as well as in CYP2D6 EMs. Most probably, one of these is CYP1A2. CYP1A2 is one of the major enzymes involved in the metabolism of fluvoxamine [5], and saturation kinetics have been demonstrated for other drugs metabolised by this enzyme, such as theophylline and caffeine [14, 15]. The finding that the r values for the correlation between CYP1A2 metabolic ratio and fluvoxamine AUC at the doses of 100 and 200 mg day⁻¹ were closer to zero than the corresponding r values at lower doses might also indicate that CYP1A2 gradually becomes saturated with increasing fluvoxamine doses.

In CYP2D6 EMs, the other enzyme involved might be CYP2D6 [6], which is also characterized by saturation kinetics [17]. However, the finding that CYP2D6 PMs also had curvilinear plots with the negative slope decreasing indicates that at least one other, non-CYP1A2, non-CYP2D6 pathway, is involved in the metabolism of fluvoxamine. This pathway is most likely not CYP2C19 [6]. The reason why the two CYP2D6 PMs had AUC values in the same range as the EMs might be that they underwent a faster metabolism via other enzyme systems; in fact, the PM tested was the second fastest caffeine metaboliser. Model fitting with the Michaelis-Menten equation to ascertain V_{max} and K_m values was considered not meaningful due to the small number of data points available from each

Figure 4 Correlation between number of suspected adverse drug reactions reported during 1 week of treatment with fluvoxamine 200 mg day⁻¹ and trough steady-state serum fluvoxamine concentrations at the end of the same week ($r=0.62$; $P=0.057$).

subject and due to the complex situation when two different saturable processes (CYP1A2 and CYP2D6) with different $V_{\max}$ and K_m values might occur concomitantly in addition to a presumably non-saturable low-affinity metabolic pathway.

We found a close to significant positive correlation between the number of suspected adverse effects reported during week 4 and trough fluvoxamine serum concentrations at the end of the same week, indicating that a concentration-adverse drug reaction relationship might exist. At a dose of 200 mg day^{-1} , there was no clear cut-off serum concentration below which adverse effects were not present. However, on the other hand, the relative lack of adverse effects at the doses $25\text{--}50 \text{ mg day}^{-1}$ strongly indicate that the occurrence of adverse drug reactions is dose and concentration dependent within the individuals, although the influence of time factors cannot be completely ruled out. A concentration-adverse drug reaction relationship has also been observed in a study of 18 patients with major depression treated with fluvoxamine $100\text{--}300 \text{ mg day}^{-1}$ for 4 weeks [27]. In contrast, no concentration-adverse drug reaction effect relationships were revealed in two other studies [28, 29], but the methodology for the detection of adverse effects in these studies is insufficiently described.

In conclusion, the present study clearly demonstrates that fluvoxamine exhibits non-linear kinetics within the therapeutic dose interval. The reason for non-linearity is not Michaelis-Menten saturation kinetics of a single metabolic pathway, but rather a more complex metabolic picture with multiple pathways involved. The clinical implications of these findings are two-fold: First, changes in fluvoxamine dosage cause disproportionate changes in the serum levels of fluvoxamine. Although fluvoxamine has a broad therapeutic range [1, 2], the results from the present study as well as from another study [27] indicate that higher serum concentrations are associated with more adverse effects. Therefore, large and sudden increases in maintenance doses of fluvoxamine should preferably be avoided. Second, the present study confirms the finding from a case report [20], indicating that a disproportionate extension of the recovery time may occur in cases of fluvoxamine intoxications.

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