

PHARMACOKINETICS AND DISPOSITION

U. Jeppesen · L. F. Gram · K. Vistisen · S. Loft
H. E. Poulsen · K. Brøsen

Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine

Received: 11 December 1995 / Accepted in revised form: 29 February 1996

Abstract Objectives: The purpose of this pharmacokinetic study was to investigate the dose-dependent inhibition of model substrates for CYP2D6, CYP2C19 and CYP1A2 by four marketed selective serotonin reuptake inhibitors (SSRIs): citalopram, fluoxetine, fluvoxamine and paroxetine.

Methods: The study was carried out as an in vivo single-dose study including 24 young, healthy men. All volunteers had been identified as sparteine- and mephenytoin-extensive metabolisers. The volunteers received in randomised order, at weekly intervals, increasing single oral doses of one of the four SSRIs, followed 3 h later by sparteine (CYP2D6), mephenytoin (CYP2C19) and caffeine (CYP1A2) tests. Fluoxetine was given at 3-week intervals because of the long half-life of fluoxetine and its metabolite norfluoxetine. Citalopram, fluoxetine and paroxetine were given in doses of 10, 20, 40 and 80 mg and fluvoxamine was given in doses of 25, 50, 100 and 200 mg.

Results: With increasing doses, there was a statistically significant increase in the sparteine metabolic ratio (MR) ($P < 0.01$, Page's test for trend) for all four SSRIs. The increase was modest after intake of citalopram and fluvoxamine, while the increase was more pronounced after fluoxetine intake, although no volunteers changed phenotype from extensive metabolisers to poor metabolisers. Three of the six volunteers changed phenotype from extensive metabolisers to poor metabolisers after intake of 40 or 80 mg paroxetine. There was a statistically significant increase in the mephenytoin *S/R* ratio ($P < 0.01$, Page's test for trend) with increasing doses of fluoxetine and fluvoxamine, but not after

citalopram and paroxetine. However, no volunteers changed phenotype from extensive to poor metabolisers of *S*-mephenytoin. After intake of fluvoxamine, the urinary excretion of the metabolites related to N3 demethylation of caffeine were below the limit of quantification, whereas there were no significant changes in the urinary caffeine metabolic ratios after intake of the other three SSRIs.

Conclusion: This investigation confirms that paroxetine and fluoxetine are potent inhibitors of CYP2D6, that fluvoxamine and fluoxetine are moderate inhibitors of CYP2C19 and that fluvoxamine is a potent inhibitor of CYP1A2 in humans in vivo. The clinical prediction of interaction from single-dose experiments may have to take the degree of accumulation during steady-state after multiple doses into account.

Key words SSRIs, CYP2D6, CYP2C19, CYP1A2; single dose, inhibition

Introduction

The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressants with the same pharmacodynamic effects, but with quite different chemical structures. The clinically available SSRIs are citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The elimination of these lipophilic compounds proceeds predominantly via oxidation catalysed by cytochrome P450 (CYP) in the liver. Hence, SSRIs have the potential for inhibition of CYP enzymes [1]. Paroxetine and fluoxetine are potent inhibitors of CYP2D6 [2–4], whereas the other SSRIs are less potent inhibitors [5–7]. Fluoxetine and paroxetine and to a lesser degree citalopram, fluvoxamine and sertraline have the potential to cause pharmacokinetic interactions with drugs metabolised by CYP2D6, and this has been well documented for tricyclic antidepressants as reviewed by Brosten [1]. The CYP2D6 is also important for the

U. Jeppesen (✉) · L. F. Gram · K. Brøsen
Department of Clinical Pharmacology, Institute of Medical
Biology, Odense University, Winsløwparken 19, DK-5000
Odense C, Denmark

K. Vistisen · S. Loft · H. E. Poulsen
Department of Pharmacology, University of Copenhagen,
Denmark

biotransformation of some neuroleptics, beta-adrenoceptor blockers and some antiarrhythmics [8].

A second CYP enzyme, CYP2C19, is the source of the *S*-mephenytoin oxidation polymorphism [9, 10]. The CYP2C19 is important for the biotransformation of amitriptyline [11], citalopram [7], clomipramine [12], diazepam and *N*-desmethyldiazepam [13], imipramine [14], mephobarbital [15], moclobemide [16], omeprazole [17] and for the prodrug proguanil [18]. The inhibition of CYP2C19 by SSRIs has been studied neither in vitro nor in vivo.

Fluvoxamine but not the other SSRIs has been shown to be a very potent inhibitor of CYP1A2 in vitro [19, 20]. Thus, fluvoxamine has the potential to cause a pharmacokinetic interaction with drugs metabolised by CYP1A2, and indeed this has been reported for clomipramine [21], clozapine [22, 23], imipramine [24, 25], propranolol [26] and theophylline [27–29]. The other SSRIs are less likely to inhibit CYP1A2 in vivo, but experimental data in support of this notion are lacking.

In general, the inhibition of a CYP enzyme by an SSRI is determined by the affinity of the drug for the enzyme, by the dose and the plasma concentration and by whether the SSRI is administered as a single dose or given repeatedly.

The aim of the present study was to screen the dose-dependent inhibition of CYP2D6, CYP2C19 and CYP1A2 by the four SSRIs citalopram, fluoxetine, fluvoxamine and paroxetine in a setting with single-dose experiments in healthy volunteers. For technical reasons, the fifth marketed SSRI, sertraline, could not be included.

Materials and methods

Study population

The study was carried out as an open, randomised study including 24 volunteers selected from a database of approximately 1600 healthy, Danish subjects phenotyped with regard to sparteine and mephenytoin oxidation. The subjects were men with a median age of 25 years (range 20–37 years), and they were extensive metabolisers (EMs) of both sparteine and *S*-mephenytoin. The phenotype assignment was confirmed in all subjects by a prestudy sparteine and mephenytoin test in combination with a caffeine test. No subjects had heart, liver, or kidney disease according to medical history, clinical examination, biochemistry/haematology screening and ECG examination. None of the volunteers consumed alcohol or drugs on a regular basis at the time of the study. During the study period, no other drugs than test drugs were allowed. Intake of coffee, tea and Coca Cola was not allowed for the last 19 h before the caffeine test was started. All men were non-smokers. The volunteers consented to participate in the study on the basis of verbal and written information, and the study was approved by the regional Ethics Committee and by the Danish National Board of Health.

Study procedure

The inhibition of the metabolism of sparteine, mephenytoin and

caffeine by different doses of the four SSRIs: citalopram (Cipramil, Lundbeck Pharma, Denmark), fluoxetine (Fontex, Eli Lilly, Denmark), fluvoxamine (Fevarin, Solvay Duphar BV, Netherlands) and paroxetine (Seroxat, Novo Nordisk Pharma, Denmark) was determined. The volunteers were randomised into four groups, one for each of the SSRIs. At weekly intervals, each group received a single, oral dose of one of the four SSRIs. The dose was doubled every week for citalopram, fluvoxamine and paroxetine and every 3 weeks for fluoxetine followed by sparteine, mephenytoin and caffeine testing. Citalopram, fluoxetine and paroxetine were given in single doses of 10, 20, 40 and 80 mg and fluvoxamine was given in single doses of 25, 50, 100 and 200 mg. Three hours after each ingestion of an SSRI, the volunteer emptied the bladder, and test doses of sparteine [a tablet of 100 mg sparteine (Depasan, Giuliani, Hannover, Germany)], mephenytoin [a tablet of 100 mg mephenytoin (Mesantoin, Sandoz, Basel, Switzerland)] and caffeine (two cups of coffee) were given. The urine was collected for the following 12 h, and 4 h after test dose ingestion 5 ml urine was voided in a conical glass tube with 100 µl 2 N HCl (in order to conserve the caffeine metabolite: AFMU) for the determination of the caffeine metabolites. The 12-h urine volume was recorded and 10 ml urine was stored for sparteine and mephenytoin analysis. Urine samples were kept frozen at –20 °C until analysis. An open questionnaire on adverse effects was used before, during and after the course of the study.

Analytical methods

Sparteine and its metabolites (2,3- and 5,6-dehydrosparteine) in urine were assayed by gas chromatography by the method described by Vinks [30]. For both sparteine and dehydrosparteines, the lower level of detection was 0.25 µmol·l⁻¹.

The chromatographic peak areas of *S*- and *R*-mephenytoin in urine were assayed by gas chromatography [31].

Five metabolites of caffeine: 5-acetyl-6-formylamino-3-uracil (AFMU), 1-methylxanthine (1X), 1-methyluric acid (1 U), 1,7-dimethylxanthine (17X) and 1,7-dimethyluric acid (17 U), were assayed by a standard high-performance liquid chromatography HPLC method [32, 33]. The method was modified by using gradient elution. The solvents used for elution were A: 0.05% acetic acid containing 6.5% methanol (v/v), pH = 3.20, and B: 0.05% acetic acid containing 20% methanol, pH = 7.00. Typical conditions for elution were 0% B (0–10 min), 0–40% B (10–28 min), 40–50% B (28–32 min), 50–0% B (32–35 min) and 0% B (35–45 min). The analytical intraday coefficient of variation of the metabolic ratio was 4.5%. Due to very low excretion of caffeine metabolites, the urine samples collected after fluvoxamine intake were reanalysed with an optimised HPLC assay [34].

Pharmacokinetics

The sparteine metabolic ratio (MR), a measure of CYP2D6, was calculated in the 12-h urine as follows:

$$\text{MR} = \frac{\% \text{ of dose excreted as sparteine in 12-hour urine}}{\% \text{ of dose excreted as 2,3- + 5,6-dehydrosparteine}}$$

At baseline, the MR for the volunteers ranged from 0.17 to 0.89 and one had an MR at 2.2, and, accordingly, they were all phenotyped as extensive metabolisers [35]. The *S/R* ratio of mephenytoin, a measure of CYP2C19, was calculated as the ratio between the chromatographic peak area ratios in the 12-h urine:

$$S/R \text{ ratio} = \frac{(S)\text{-mephenytoin}}{(R)\text{-mephenytoin}}$$

At baseline, the mephenytoin *S/R* ratio for the volunteers ranged from 0.03 to 0.39, and hence all subjects were phenotyped as exten-

sive metabolisers of *S*-mephenytoin [31, 36]. The urinary caffeine metabolic ratio (CMR), a measure of CYP1A2 [37], was calculated as:

$$\text{CMR} = \frac{\text{AFMU} + 1\text{X} + 1\text{U}}{17\text{U}}$$

The three pharmacokinetic indices were determined before the investigation and after each of the four single doses of the SSRIs. The combined intake of sparteine and mephenytoin does not interfere with the test results [36].

Statistics

The statistical analyses were carried out with the Page test for trend for each of the four SSRIs and by Wilcoxon's signed ranks test for pair differences, by use of the Medstat program package, version 2.1 (Astra Group, Albertslund, Denmark 1988).

Results

The sparteine metabolic ratios after intake of the four SSRIs are shown in Fig. 1. For all of the SSRIs, there was a statistically significant increase in the MR ($P < 0.01$, Page's test for trend). The increase was modest after intake of citalopram and fluvoxamine, and more pronounced after fluoxetine and especially after paroxetine. With citalopram, fluvoxamine and fluoxetine, the MR never exceeded 20, and hence no subject changed phenotype from extensive metaboliser to poor metaboliser [35]. With paroxetine, there were three subjects that changed phenotype from extensive metabolisers to poor metabolisers after 40 and 80 mg (Fig. 1).

The results regarding the mephenytoin test are shown in Fig. 2. The mephenytoin *S/R* ratio increased statistically significantly ($P < 0.01$, Page's test for trend) after fluoxetine and fluvoxamine. Even at the highest fluoxetine and fluvoxamine doses, the mephenytoin *S/R*-ratio did not exceed 0.6 and no subject thus changed phenotype to mephenytoin poor metaboliser [31]. No statistically significant trend was seen after citalopram or paroxetine. The results of the caffeine tests and the urinary caffeine metabolic ratio CMR: $\text{AFMU} + 1\text{X} + 1\text{U} / 17\text{U}$ (standard HPLC method), after intake of the four SSRIs are shown in Fig. 3. After fluvoxamine, the level of the relevant caffeine metabolites was below the limit of quantification ($10\text{--}25 \mu\text{mol} \cdot \text{l}^{-1}$). By optimising the HPLC method used in a subsequent study [34], the caffeine metabolites could be quantitated in the samples after fluvoxamine. The median CMR before treatment with fluvoxamine was 4.3 (range: 1.3–11.3) and after 25 mg fluvoxamine the median was 2.8 (range: 2.6–17), but the difference was not statistically significant ($P = 0.2$, Wilcoxon's test), and the 17U concentration, which is the denominator in the ratio, was very low ($1.5\text{--}15 \mu\text{mol} \cdot \text{l}^{-1}$) after fluvoxamine. By using another urinary caffeine metabolic ratio, $17\text{X}/137\text{X}$ [38], the

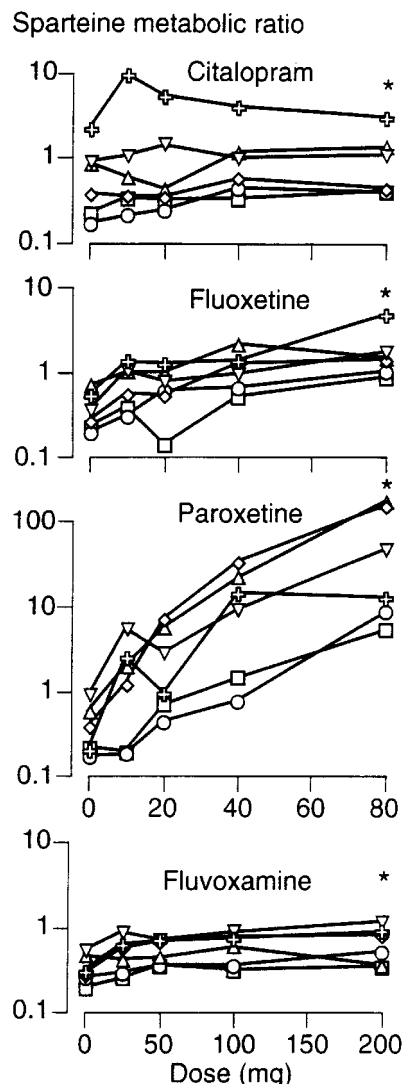


Fig. 1 Influence on CYP2D6 activity, estimated by the sparteine metabolic ratio after intake of increasing single doses of selective serotonin reuptake inhibitors. *Symbol* signifies different volunteers and these volunteers differ for each of the SSRIs. * $P < 0.05$, Page test for trend

median before fluvoxamine treatment was 1.2 (range: 0.7–6.3) but after 25 mg fluvoxamine it was reduced to 0.4 (range: 0.3–1.0) ($P \leq 0.05$, Wilcoxon's test). After fluvoxamine doses of 50–200 mg, there were no further changes in the ratio ($P > 0.05$, Page's test for trend). The CMR did not change after citalopram, fluoxetine or paroxetine (Fig. 3).

Discussion

The present study confirmed that fluoxetine and paroxetine are potent inhibitors of CYP2D6 (Fig. 1), and this is in agreement with previous studies [1]. Our data suggest that paroxetine is more potent than fluoxetine in inhibiting CYP2D6. This is not consistent with the

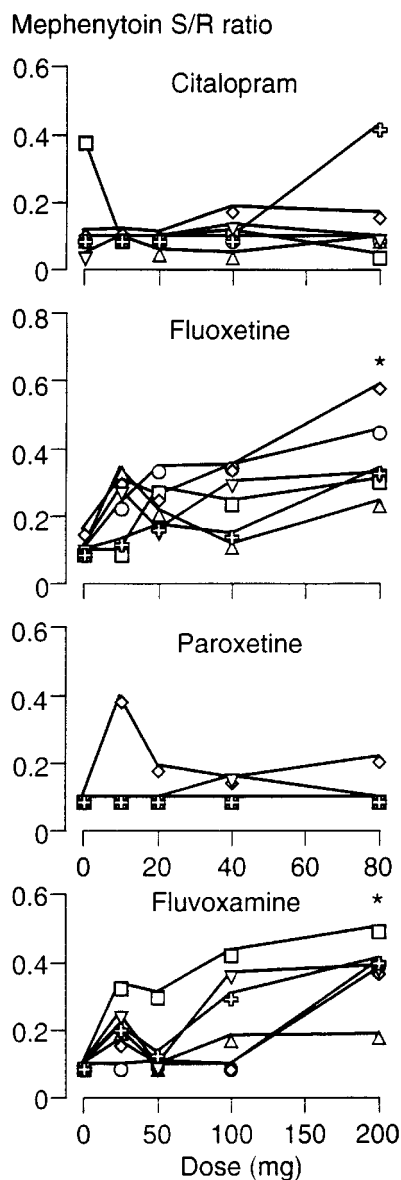


Fig. 2 Influence on CYP2C19 activity, estimated by the mephenytoin *S/R* ratio after intake of increasing single doses of selective serotonin reuptake inhibitors. *Symbol* signifies different volunteers and these volunteers differ for each of the SSRIs. * $P < 0.05$, Page test for trend

findings of earlier studies using desipramine as a substrate for CYP2D6, showing that the two SSRIs in repeated dosing of 20 mg day⁻¹ are equally potent inhibitors [39–41]. The discrepancy between the present and the previous studies could be that fluoxetine and its active metabolite norfluoxetine continue to accumulate for several weeks due to their very long half-lives [42]. Fluvoxamine and citalopram are less potent inhibitors of CYP2D6 both in vitro and in vivo and this was confirmed here (Fig. 1).

The present study showed (Fig. 2) that fluoxetine and fluvoxamine were moderate inhibitors of the *S*-mephenytoin metabolism, although none of the subjects changed phenotype from *S*-mephenytoin extensive

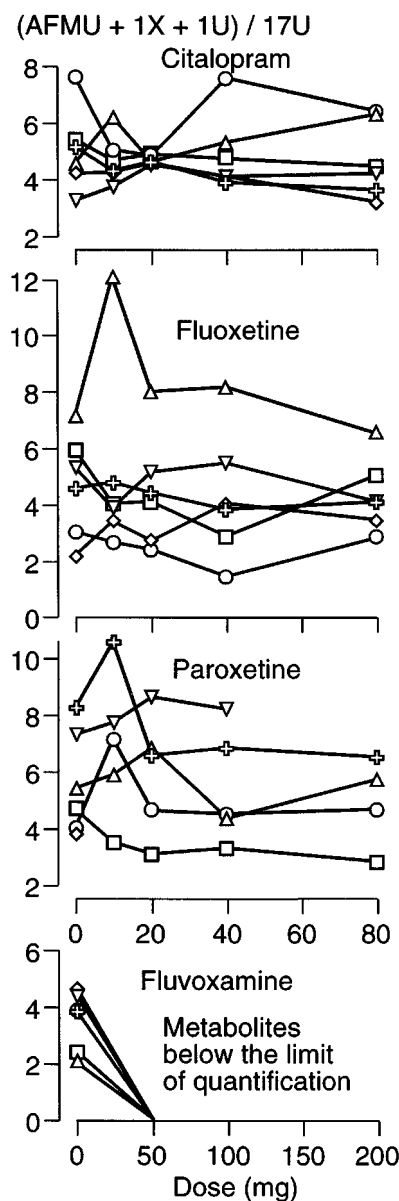


Fig. 3 Influence on the CYP1A2 activity, estimated by the caffeine metabolic ratio (AFMU+1X+1U/17U) after intake of increasing single doses of selective serotonin reuptake inhibitors. *Symbol* signifies different volunteers and these volunteers differ for each of the SSRIs

metaboliser to poor metaboliser. Hence, the two drugs may have some potential for causing pharmacokinetic interactions with other substrates of CYP2C19. Neither citalopram nor paroxetine seemed to inhibit CYP2C19 (Fig. 2), and with citalopram this is somewhat surprising because citalopram is metabolised by this CYP enzyme [7].

With the standard HPLC method applied in the present study, the metabolites resulting from N3 demethylation of caffeine were excreted in amounts below the limit of quantification after fluvoxamine (Fig. 3), and after optimisation of the method only very low metabolite levels were detected. This supports the notion from

in vitro studies that fluvoxamine is a very potent inhibitor of the CYP1A2 and thus of N3 demethylation of caffeine [19, 43–45].

In a subsequent study, we showed that caffeine clearance decreased from $107 \text{ ml} \cdot \text{min}^{-1}$ to $21 \text{ ml} \cdot \text{min}^{-1}$, and that the elimination half-life increased from 5 h to 31 h during daily intake of 100 mg fluvoxamine [34]. The CYP1A2 activity appears to be almost completely abolished after a single oral dose of 50 mg day^{-1} . As expected from studies with human liver microsomes [5, 19, 20], neither citalopram, fluoxetine nor paroxetine inhibited CYP1A2 (Fig. 3). Thus, in contrast to fluvoxamine, these SSRIs will not cause pharmacokinetic interactions with drugs that are metabolised by CYP1A2.

Thus, paroxetine and fluoxetine are the only SSRIs that will cause clinically important interactions with drugs metabolised by CYP2D6, and fluvoxamine is the only SSRI that will cause clinically important interaction with drugs metabolised by CYP1A2. At clinical maintenance doses, the inhibitory effects of fluoxetine (CYP2D6), paroxetine (CYP2D6) and fluvoxamine (CYP1A2) will be almost complete. Due to the pronounced accumulation of fluoxetine/norfluoxetine, the inhibitory effect after the single doses employed in this study will be less than maximal. Fluoxetine and fluvoxamine may cause clinically important interactions with drugs metabolised by CYP2C19, but this needs to be further elucidated.

Acknowledgements This work was supported by grants from the Danish Medical Research Council (Grant No. 12–9206).

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