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In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine

ZHEN-HUA XU, HONG-GUANG XIE & HONG-HAO ZHOU
Pharmacogenetics Research Institute, Hunan Medical University, Changsha, Hunan 410078, China

Studies were performed in eight healthy extensive metabolizers of mephenytoin and debrisoquine to determine the effect of fluvoxamine on the activities of S-mephenytoin 4′-hydroxylase (CYP2C19) and metoprolol α-hydroxylase (CYP2D6). Therapeutic dosing with fluvoxamine (100 mg day^{-1}) for 2 weeks caused a significant increase in the 0–8 h urinary S/R ratio of mephenytoin from 0.16 to 0.55 (95% confidence interval for difference between means: 0.28–0.50; $P<0.01$), accompanied by a 54% reduction in the 0–8 h urinary recovery of 4′-hydroxymephenytoin (95% confidence interval for difference between means: 3.64–16.24 mg; $P<0.05$). However, this did not alter the assigned phenotype of any of the subjects based on the established antimode of 0.95 (S/R-mephenytoin ratio). Two weeks after fluvoxamine was discontinued, both metabolic indices returned to their pre-study values. By contrast, fluvoxamine had no effect on either 0–8 h urinary metoprolol/α-hydroxymetoprolol ratio (95% confidence interval for difference between means: −0.38–0.46; $P>0.05$) or the 0–8 h urinary recovery of α-hydroxymetoprolol (95% confidence interval for difference between means: −0.61–0.70 mg; $P>0.05$). These results indicated fluvoxamine has a modest inhibitory effect on the activity of CYP2C19, but no effect on that of CYP2D6 *in vivo*.

Keywords fluvoxamine mephenytoin metoprolol CYP2D6 CYP2C19 inhibition

Introduction

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is widely used in the treatment of major depression and other affective disorders [1]. Previous studies have shown that concomitant intake of fluvoxamine can result in clinically relevant interactions with many drugs including imipramine [2, 3], clomipramine [4], amitriptyline [5, 6], clozapine [7], theophylline [8, 9], propranolol [1], diazepam [10], alprazolam [11, 12] and carbamazepine [13]. These interactions have been attributed to impairment of different cytochrome P450 activities. Since fluvoxamine is a highly potent inhibitor of CYP1A2 (K_i = 0.12–0.24 μM) in human liver microsomes *in vitro* [14], impairment of CYP1A2 activity is likely to be the cause of the *in vivo* interactions between fluvoxamine and substrates for CYP1A2, such as imipramine [15], clozapine [16], theophylline [17] and propranolol [18]. However, during coadministration of fluvoxamine, the clearances of amitriptyline, alprazolam and carbamazepine, which are mainly oxidized by CYP3A4 [6, 12, 19], are also decreased. These data suggest that fluvoxamine also inhibits CYP3A4 activity. In addition to the involvement of CYP1A2 and CYP3A4, the demethylation of imipramine, clomipramine and amitriptyline appears to be partially mediated both *in vivo* and *in vitro* by mephenytoin 4′-hydroxylase [20–23] , now known to be CYP2C19 [24]. Furthermore, fluvoxamine also inhibits the biotransformation of diazepam and its N-demethylated metabolite, nordiazepam [10], which are putative substrates for CYP2C19 [25]. Thus, CYP2C19 may also be involved in the interactions between imipramine, amitriptyline, diazepam and fluvoxamine.

To our knowledge, there are no published data describing the possible effect of fluvoxamine on CYP2C19 either *in vivo* or *in vitro* although other SSRIs

Correspondence: Professor Hong-Hao Zhou, Pharmacogenetics Research Institute, Hunan Medical University, Changsha, Hunan 410078, China

have been tested *in vitro* [26]. Fluvoxamine has been found to inhibit CYP2D6 activity in human liver microsomes [27], but whether inhibition occurs *in vivo* has not been tested. The present study was designed to determine the effect of fluvoxamine on the activities of CYP2C19 and CYP2D6 in healthy volunteers using mephenytoin and metoprolol as probe drugs.

Methods

Eight male volunteers previously phenotyped as extensive metabolizers of both mephenytoin and debrisoquine, were recruited. Their age and weight were 21.7 ± 1.6 (mean $\pm$ s.d.) years and 59.8 ± 6.5 kg. All subjects were non-smokers and in good health according to clinical history, physical examination and routine laboratory tests. No medication or ethanol consumption was allowed at least 2 weeks prior to or during the study. The study was approved by the Academic Committee and the Ethics Committee of Hunan Medical University and informed, written consent was obtained from the subjects.

All subjects were given oral fluvoxamine (Fevarin®; Duphar, Weesp, The Netherlands) at the normal therapeutic dose of 100 mg day^{-1} for 2 weeks. The subjects were phenotyped with mephenytoin and metoprolol on the day prior to the study, 2 h after the last dose of fluvoxamine and 2 weeks after discontinuation of fluvoxamine. After an overnight fast, each subject received 100 mg mephenytoin (Mesantoin®, Sandoz) and 100 mg metoprolol (Betaloc®, Sino-Swed Pharmaceutical Co. Ltd) orally with 250 ml water. Urine was then collected for the next 8 h and aliquots stored at -20° C until analyzed.

The urinary mephenytoin S/R ratio was determined by gas chromatography using a chiral capillary column [28]. Urine was analyzed for 4′-hydroxymephenytoin, metoprolol and α-hydroxymetoprolol by h.p.l.c. [29, 30]. Data were compared using the Wilcoxon signed rank test with the level of significance set at $P < 0.05$.

Results

Administration of a therapeutic dose of fluvoxamine (100 mg day^{-1}) for 2 weeks caused a significant increase in the 0–8 h urinary S/R ratio of mephenytoin from 0.16 to 0.55 (95% confidence interval for difference between means: 0.28–0.50; $P < 0.01$). This change was accompanied by a 54% reduction in the 0–8 h urinary excretion of 4′-hydroxymephenytoin from 18.5 mg to 8.5 mg (95% confidence interval for difference between means: 3.64–16.24 mg; $P < 0.05$) (Figure 1). However, based on established antimodes for the distribution of the S/R ratio (0.95) and the 0–8 h 4′-hydroxymephenytoin (5% of dose), fluvoxamine did not convert these values to those of a CYP2C19 poor metabolizer in any of the subjects. Two weeks after discontinuation of fluvoxamine, both metabolic indices of mephenytoin had returned to their pre-study values.

By contrast, fluvoxamine had no effect on either the 0–8 h urinary metoprolol/α-hydroxymetoprolol ratio (95% confidence interval for difference between means: -0.38–0.46; $P > 0.05$) or the 0–8 h urinary recovery of α-hydroxymetoprolol (95% confidence interval for

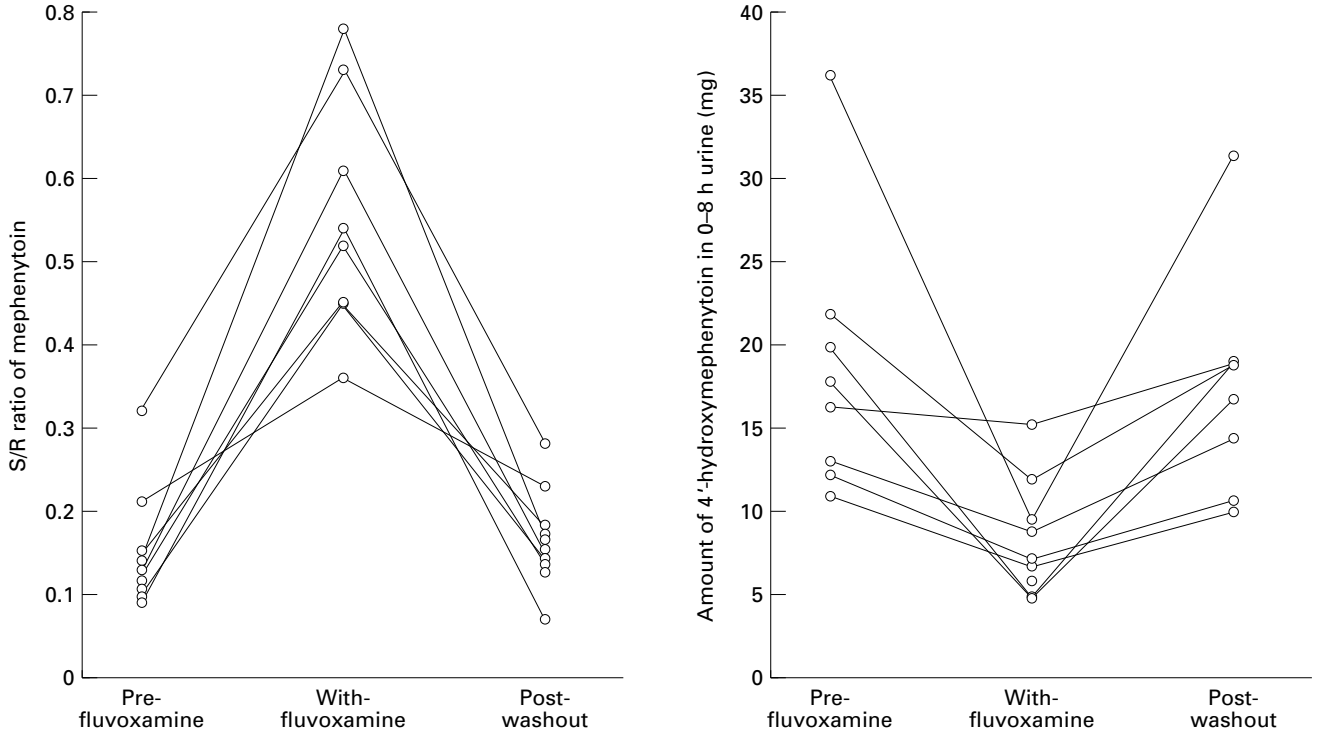

Figure 1 The effects of oral fluvoxamine (100 mg day^{-1} for 2 weeks) on the urinary S/R ratio of mephenytoin (left) and on the 0–8 h recovery of 4′-hydroxymephenytoin (right) after oral administration of 100 mg racemic mephenytoin. All subjects were extensive metabolizers of mephenytoin.

differences between means: −0.61–0.70 mg; $P > 0.05$) (Figure 2).

Discussion

The 0–8 h urinary S/R ratio and excretion of 4′-hydroxymephenytoin after administration of an oral dose racemic mephenytoin has been demonstrated to reflect CYP2C19 activity [31]. Both the increase in S/R ratio of mephenytoin and the reduction in 4′-hydroxymephenytoin recovery in 0–8 h urine during coadministration of fluvoxamine indicate that fluvoxamine is an inhibitor of mephenytoin 4′-hydroxylase (CYP2C19). Impairment by fluvoxamine of CYP2C19 activity may contribute to the observed interactions between fluvoxamine and tricyclic antidepressants and diazepam.

It is not known which forms of cytochrome P450 metabolize fluvoxamine. Because it is an inhibitor of CYP2C19, fluvoxamine might also be a substrate for this isozyme. However, the observations that fluvoxamine is a potent inhibitor of CYP1A2 [14] and that smokers achieve significantly lower plasma concentrations of the drug compared with non-smokers [32] provide indirect evidence that CYP1A2 is the major form of cytochrome P450 involved in its metabolism.

Fluvoxamine was a weak inhibitor of CYP2D6 in human liver microsomes ($K_i = 8.2$ μM) [27]. In the present study, fluvoxamine had no effect on either the 0–8 h urinary metoprolol/α-hydroxymetoprolol ratio or the 0–8 h urinary recovery of α-hydroxymetoprolol, two indices of CYP2D6 activity [33]. Thus plasma concentrations of fluvoxamine at therapeutic doses may not be high enough to inhibit the activity of CYP2D6. This is consistent with a previous *in vivo* study in which the aromatic 2-hydroxylation of desipramine, also mediated by CYP2D6, was unaffected by fluvoxamine [2].

In summary, the present study indicates that fluvoxamine has a selective inhibitory effects on different cytochrome P450 enzymes *in vivo*.

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References

1 Benfield P, Ward A. Fluvoxamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 1986; **32**: 313–334.
2 Spina E, Pollicino AM, Avenoso A, Campo GM, Perucca E, Caputi AP. Effect of fluvoxamine on the pharmacokinetics of imipramine and desipramine in healthy subjects. *Ther Drug Monit* 1993; **15**: 243–246.
3 Skjelbo E, Brøsen K. Inhibitors of imipramine metabolism by human liver microsomes. *Br J Clin Pharmacol* 1992; **34**: 256–261.
4 Hätter S, Arand M, Oesch F, Hiemke C. Non-competitive inhibition of clomipramine N-demethylation by fluvoxamine. *Psychopharmacology* 1995; **117**: 149–153.
5 Bertschy G, Vandel S, Bandel B, Allers G, Volmat R.

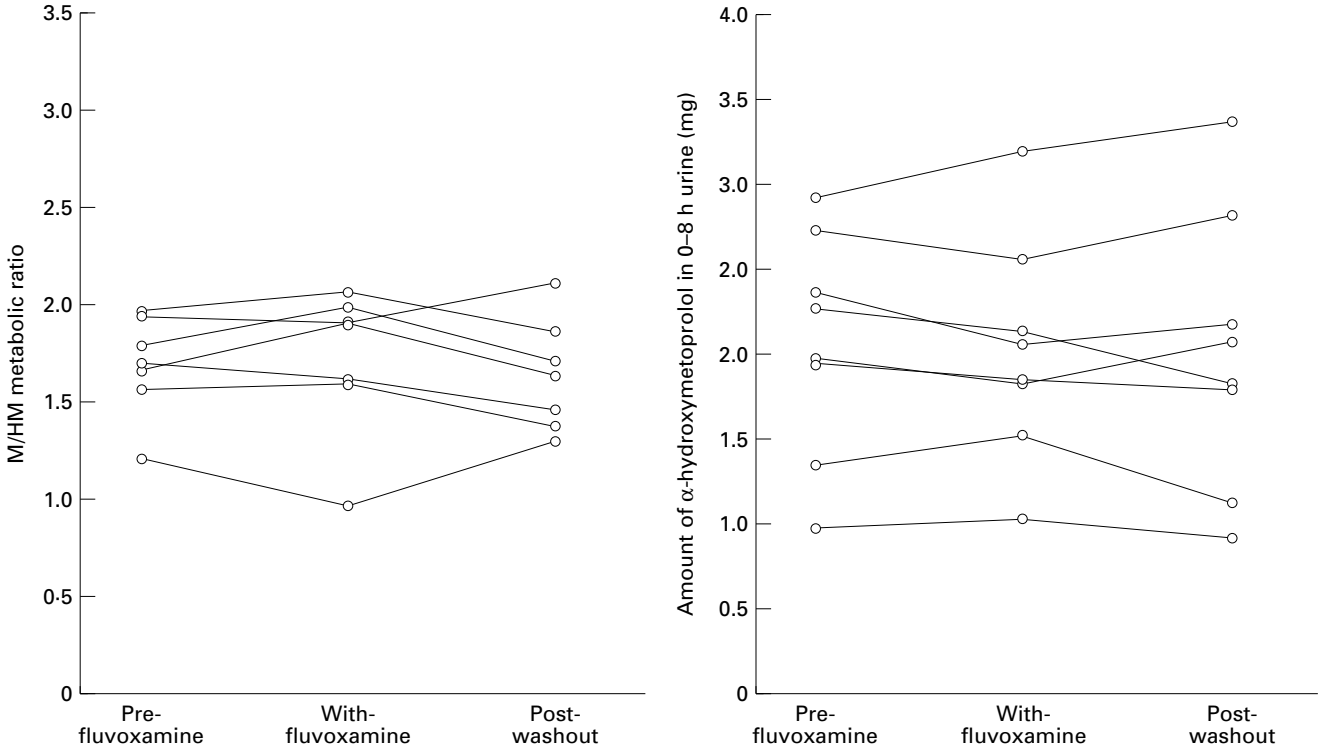

Figure 2 The effects of oral fluvoxamine (100 mg day^{-1} for 2 weeks) on the urinary metoprolol/a-hydroxymetoprolol (M/HM) ratio (left) and on the 0–8 h recovery of α-hydroxymetoprolol (right) after oral administration of 100 mg metoprolol. All subjects were extensive metabolizers of debrisoquine.

Fluvoxamine-tricyclic interaction. *Eur J Clin Pharmacol* 1991; **40**: 119–120.

6 Schmider J, Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. N-demethylation of amitriptyline in vitro: role of cytochrome P-450 3A (CYP3A) isoforms and effect of metabolic inhibitors. *J Pharmacol Exp Ther* 1995; 275: 592–597.

7 Jerling M, Lindstrom L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16**: 368–374.

8 Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* 1991; **6**: 460–462.

9 Rasmussen BB, Mäenpää J, Pelkonen O, *et al.* Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; **39**: 151–159.

10 Perucca E, Gatti G, Cipolla G, *et al.* Inhibition of diazepam metabolism by fluvoxamine: A pharmacokinetic study in normal volunteers. *Clin Pharmacol Ther* 1994; **56**: 471–476.

11 Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; **46**: 35–39.

12 von Moltke LL, Greenblatt DJ, Cotreau-Bibbo MM, Harmatz JS, Shader RI. Inhibitors of alprazolam metabolism in vitro: effect of serotonin-reuptake-inhibitor antidepressants, ketoconazole and quinidine. *Br J Clin Pharmacol* 1994; **38**: 23–31.

13 Martinelli V, Bocchetta A, Palmas AM, Zompo MD. An interaction between carbamazepine and fluvoxamine. *Br J Clin Pharmacol* 1993; **36**: 615.

14 Brøsen K, Skjelbo E, Rasmussen BB, Poulsen HE, Loft S. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 1993; **45**: 1211–1214.

15 Lemoine A, Gautier JC, Azoulay D, *et al.* Major pathway of imipramine metabolism is catalyzed by cytochrome P-450 1A2 and P-450 3A4 in human liver. *Mol Pharmacol* 1993; 43: 827–832.

16 Bertilsson L, Carrillo JA, Dahl M-L, *et al.* Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol* 1994; **38**: 471–473.

17 Robson RA, Miners JO, Matthews AP, *et al.* Characterization of theophylline metabolism by human liver microsomes. Inhibition and immunochemical studies. *Biochem Pharmacol* 1988; **37**: 1651–1659.

18 Yoshimoto K, Echizen H, Chiba K, Tani M, Ishizaki T. Identification of human CYP isoforms involved in the metabolism of propranolol enantiomers- N-desisopropylation is mediated mainly by CYP1A2. *Br J Clin Pharmacol* 1995; **39**: 421–431.

19 Pirmohamed M, Kitteringham NR, Breckenridge AM, Park BK. The effect of enzyme induction on the cytochrome P450-mediated bioactivation of carbamazepine by mouse liver microsomes. *Biochem Pharmacol* 1992; **44**: 2307–2314.

20 Skjelbo E, Gram LF, Brøsen K. The N-demethylation of imipramine correlates with the oxidation of S-mephenytoin (S/R ratio): a population study. *Br J Clin Pharmacol* 1993; **35**: 331–334.

21 Chiba K, Saitoh A, Koyama E, Tani M, Hayashi M, Ishizaki T. The role of S-mephenytoin 4′-hydroxylase in imipramine metabolism by human liver microsomes: a two-enzyme kinetic analysis of N-demethylation and 2-hydroxylation. *Br J Clin Pharmacol* 1994; **37**: 237–242.

22 Nielsen KK, Brøsen K, Jeppe Hansen MG, Gram LF. Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther* 1994; **55**: 518–527.

23 Breyer-Pfaff U, Pfandl B, Nill K, *et al.* Enantioselective amitriptyline metabolism in patients phenotyped for two cytochrome P450 isozymes. *Clin Pharmacol Ther* 1992: **52**: 350–358.

24 Goldstein JA, Faletto MB, Romkes-Sparks M, *et al.* Evidence that CYP2C19 is the major (S)-mephenytoin 4′-hydroxylase in humans. *Biochemistry* 1994; **33**: 1743–1752.

25 Bertilsson L, Henthorn TK, Sanz E, Tybring G, Säwe J, Villén T. Importance of genetic factors in the regulation of diazepam metabolism; Relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype. *Clin Pharmacol Ther* 1989; **45**: 348–355.

26 Kobayashi K, Yamamoto T, Chiba K, Tani M, Ishizaki T, Kuroiwa Y. The effects of selective reuptake inhibitors and their metabolites on S-mephenytoin 4′-hydroxylase activity in human liver microsomes. *Br J Clin Pharmacol* 1995; **40**: 481–485.

27 Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of selective serotonin reuptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 1992; **34**: 262–265.

28 Wedlund PJ, Aslanian WS, McAllister CB, Wilkinson GR, Branch RA. Mephenytoin hydroxylation deficiency in Caucasians: frequency of a new oxidative drug metabolism polymorphism. *Clin Pharmacol Ther* 1984; **36**: 773–780.

29 Xie HG, Huang SL, Zhou HH. High-performance liquid chromatographic determination of urinary 4′-hydroxymephenytoin, a metabolic marker for the hepatic enzyme CYP2C19, in humans. *J Chromatogr B* 1995; **668**: 125–131.

30 Lennard MS, Silas JH. Rapid determination of metoprolol and α-hydroxymetoprolol in human plasma and urine by high-performance liquid chromatography. *J Chromatogr* 1983; **272**: 205–209.

31 Jacqz E, Hall SD, Branch RA, Wilkinson GR. Polymorphic metabolism of mephenytoin in man: pharmacokinetic interaction with a coregulated substrate, mephobarbital. *Clin Pharmacol Ther* 1986; **39**: 646–653.

32 Spigset O, Carleborg L, Hedenmalm K, Dahlqvist R. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; **58**: 399–403.

33 McGourty JC, Silas JH, Lennard MS, Tucker GT, Woods HF. Metoprolol metabolism and debrisoquine oxidation polymorphism-population and family studies. *Br J Clin Pharmacol* 1985; **20**: 555–566.

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