Effects of Caffeine on the Kinetics of Fluvoxamine and its Major Metabolite in Plasma After a Single Oral Dose of the Drug

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Abstract: The effects of caffeine on the kinetics of fluvoxamine (FLV) and its major metabolite fluvoxamino acid (FLA) in plasma, after a single oral dose of the drug, were studied in 12 healthy male volunteers. The subjects received caffeine 300 mg/d or placebo for 11 days in a double-blind randomized crossover manner, and on the eighth day they received a single oral 50-mg dose of FLV. Blood sampling and pharmacodynamic evaluation were conducted up to 72 hours after FLV dosing. Plasma concentrations of FLV and FLA were measured by high-performance liquid chromatography. Caffeine significantly decreased the plasma concentrations at 6 time points ($P < 0.05$) and total area under the plasma concentration-time curve (156.5 ± 51.7 vs. 118.9 ± 38.2 ng/h/mL, $P < 0.01$) of FLV. Plasma concentration and pharmacokinetic parameters of FLA were not affected by caffeine. Caffeine induced no significant change in the pharmacodynamic effects of FLV. The present study suggests that caffeine slightly induces the metabolism of FLV, probably mediated by CYP1A2.

Key Words: caffeine, fluvoxamine, fluvoxamino acid, metabolism, CYP1A2

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The selective serotonin reuptake inhibitor fluvoxamine (FLV) is widely used in the treatments of depression[1] and other psychiatric disorders.[2] FLV shows similar therapeutic efficacy to tricyclic antidepressants, but fewer anticholinergic and cardiovascular side effects.[2] It has been suggested that FLV is metabolized by oxidative demethylation of the methoxy group, degradation at the amino group, and removal of the entire ethanolamino group.[3] The major metabolite in human urine is fluvoxamino acid (FLA), the product of oxidative demethylation.[3] Our previous study[4] has shown that the combined plasma concentration of FLV and FLA best predicts a good therapeutic response for depression, suggesting that FLA may contribute to the antidepressant effect during FLV treatment.

One study[5] has shown a significant correlation between the area under the plasma concentration-time curve (AUC) after a single dose of FLV and the activity of the enzyme CYP1A2. In another study,[6] cigarette smoking, an inducer of CYP1A2,[7] significantly lowered the AUC of FLV. These findings suggest that CYP1A2 is involved in the metabolism of FLV. Our recent study[8] has suggested that enoxacin, an inhibitor of CYP1A2,[9] slightly inhibits the metabolism of FLV, supporting the view that CYP1A2 is involved in FLV metabolism.

Caffeine is a low-affinity drug for CYP1A2, and may inhibit the metabolism of substrates for this enzyme.[10] In fact, there have been some reports[11–13] suggesting that caffeine inhibits the metabolism of clozapine, an atypical antipsychotic drug metabolized principally by CYP1A2.[14]

These discussions point to the possibility that caffeine affects the pharmacokinetics of FLV. Therefore, the present study was undertaken to investigate the effects of caffeine on the plasma kinetics of FLV and its major metabolite FLA after a single oral dose of the drug.

MATERIALS AND METHODS

Subjects

The subjects were 12 healthy male volunteers. Their mean ± SD age was 29.6 ± 4.8 years, and their body weight was 68.3 ± 8.3 kg. Six subjects were smokers (≥ 10 cigarettes/d), and 6 subjects were nonsmokers. The study protocol was approved by the Ethics Committees of Yamagata University School of Medicine and Hirosaki University School of Medicine, and each subject gave his written informed consent to participate.

Study Design

The study was conducted in a double-blind randomized crossover manner, with at least a 6-week washout period between the 2 phases. The subjects were randomly allocated to 1 of the 2 treatment sequences, placebo-/caffeine or caffeine-/placebo. Consumption of drink or

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food that contained caffeine was prohibited from 1 week before until the end of the study. The smokers were instructed to smoke as usual during the study period. One 150-mg capsule of caffeine or matched placebo was given orally at 0800 and 2000 for 11 days. After an overnight fast at 0900 of the eighth day, 1 50-mg tablet of FLV (Luvox; Astellas Pharma Inc, Tokyo, Japan) was given orally with 100 mL of tap water. No food was allowed until 3 hours after FLV dosing. Blood samples (10 mL each) were collected into heparinized tubes before and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours after FLV dosing. Plasma was separated and stored frozen until analyzed. At the times of blood sampling, pharmacodynamic evaluation was conducted using the Digit Symbol Substitution Test (DSST), adapted from the Wechsler Adult Intelligence Scale[15] in 90 seconds, the Stanford Sleepiness Scale (SSS),[16] and the Udvalg for kliniske undersøgeler (UKU) Side Effect Rating Scale.[17] Nine items, that is, asthenia, tremor, accommodation disturbances, reduced salivation, nausea, orthostatic dizziness, palpitation, increased tendency to sweating, and headache were selected from the UKU Scale to rate side effects of FLV.

CYP2D6 Genotyping

DNA was extracted from peripheral leukocytes using a QIAamp DNA Blood Kit (Qiagen, Tokyo, Japan). The CYP2D6 *3 (*3), CYP2D6*4 (*4), and CYP2D6*5 (*5) alleles causing absent enzyme activity, and the CYP2D6*10 (*10) allele causing decreased enzyme activity were detected by previously described polymerase chain reaction methods.[18–20] Alleles that were not *3, *4, *5, or *10 were called the wild-type CYP2D6*1 (*1) allele.

Drug Measurement

Plasma concentrations of FLV and FLA were measured in duplicate by a high-performance liquid chromatography method developed in our laboratory.[21] The lowest limits of detection of FLV and FLA were 0.4 and 0.3 ng/mL, respectively. The interassay coefficient of variation of FLV was 6.3% at a concentration of 1.2 ng/mL, and that of FLA was 6.5% at a concentration of 0.9 ng/mL.

Pharmacokinetic and Pharmacodynamic Parameters

For FLV, the elimination rate constant (k) was estimated from the linear regression analysis of the terminal log-linear plasma concentration-time curve. The elimination half-life ($t_{1/2}$) was calculated from $0.693/k$. For 21 out of the 24 administrations, FLV was measurable up to 36 hours. For these administrations, the AUC from 0 hour to infinity [AUC (0 to ∞)], or total AUC, was calculated from AUC (0 to 36) + C36/k, in which C36 was the plasma concentration at 36 hours. For the remaining 3 administrations, FLV was measurable up to 48 hours and the total AUC was calculated from AUC (0 to 48) + C48/k. The mean residual AUC from the last measurement point to infinity, as a percentage of total AUC, was 12.7%.

For FLA, the AUC (0 to 12) was calculated, because it was measurable only up to 12 hours after most of the administrations (17 out of the 24 doses).

For both compounds, the AUC was calculated by the trapezoidal rule. The peak plasma concentration (C_{max}) and the time to C_{max} (T_{max}) were determined graphically.

For the DSST and SSS, the area under the score-time curve from 0 to 36 hours was calculated.

Statistical Analyses

The paired t test was used to examine whether there were significant differences between the placebo and caffeine phases in the mean plasma concentrations and pharmacokinetic parameters of FLV and FLA, and pharmacodynamic parameters. A P value of 0.05 or less was considered statistically significant.

RESULTS

Four subjects were homozygous for the 1* allele, and 8 subjects were heterozygous for the *1 and *10 alleles. Thus, it was confirmed that none of the subjects was a poor metabolizer of CYP2D6.

The mean plasma concentrations of FLV during treatment with placebo or caffeine are shown in Figure 1, and those of FLA are shown in Figure 2. The pharmacokinetic parameters of FLV and FLA are presented in Table 1. Caffeine significantly ($P < 0.05$) decreased the plasma concentrations of FLV at 1, 2, 6, 8, 24, and 36 hours (Fig. 1). Caffeine significantly ($P < 0.01$) decreased the total AUC, but did not change the C_{max} or

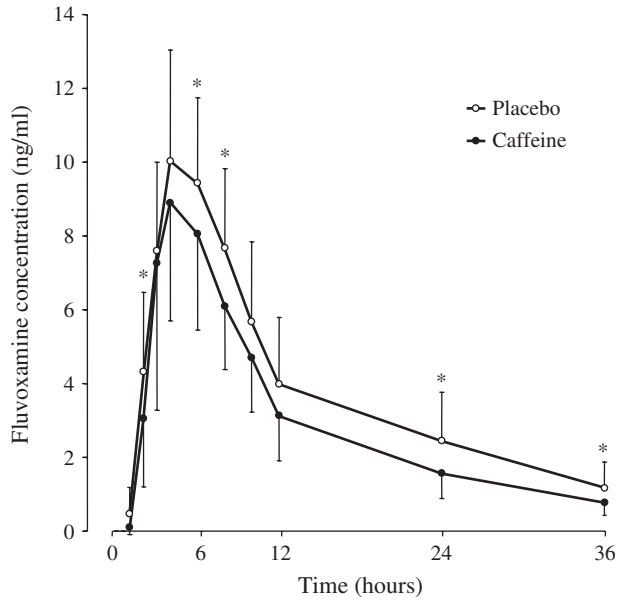

FIGURE 1. Mean plasma concentrations of FLV after a single oral 50-mg dose of FLV during the treatment with placebo (○) or caffeine (●). *P<0.05.

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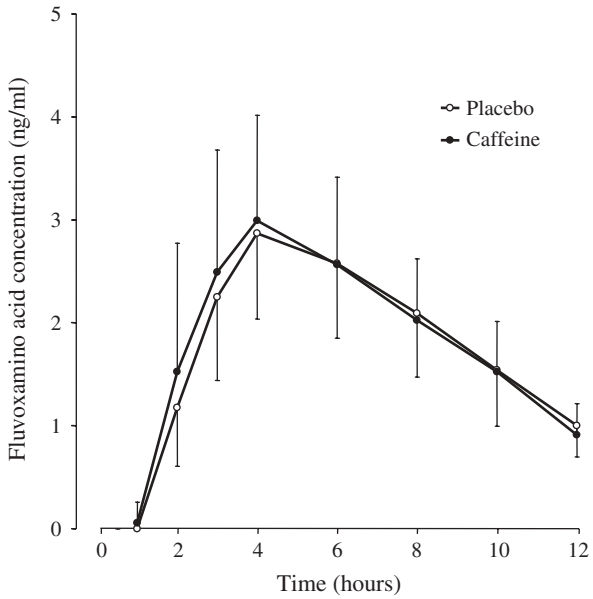

FIGURE 2. Mean plasma concentrations of FLA after a single oral 50-mg dose of FLV during the treatment with placebo (○) or caffeine (●).

elimination $t_{1/2}$ of FLV (Table 1). When the subjects were divided into 2 groups according to smoking status, the effect of caffeine on the total AUC was significant in smokers ($P < 0.05$), but not in nonsmokers ($P < 0.1$). Plasma concentration (Fig. 2) and pharmacokinetic parameters (Table 1) of FLA were not affected by caffeine. The AUC ratio of FLA to FLV was not different between the 2 phases (Table 1).

There was no significant difference between the 2 phases in the scores of DSST and SSS at any time point. The area under the score-time curve (0 to 36) of DSST and SSS were not significantly different between the 2 phases (Table 1). No subject complained of other side effects of FLV selected from the UKU Scale during the 2 phases.

TABLE 1. Pharmacokinetic Parameters of FLV and FLA and Pharmacodynamic Parameters After a Single Oral 50-mg Dose of FLV

	Placebo	Caffeine
Pharmacokinetic parameters		
FLV		
C_{max} (ng/mL)	10.6 ± 2.8	9.3 ± 3.5
T_{max} (h)	4.4 ± 1.0	4.1 ± 0.7
Total AUC (ngh/mL)	156.5 ± 51.7	118.9 ± 38.2*
Elimination $t_{1/2}$ (h)	12.7 ± 2.6	11.5 ± 2.2
FLA		
C_{max} (ng/mL)	3.0 ± 0.8	3.2 ± 1.2
T_{max} (h)	4.0 ± 0.7	3.9 ± 0.8
AUC (0 to 12) (ngh/mL)	21.1 ± 5.6	21.7 ± 7.2
AUC-ratio of FLA to FLV	0.15 ± 0.07	0.19 ± 0.07
Pharmacodynamic parameters		
AUSC (0 to 36) of DSST	3575.1 ± 443.7	3664.4 ± 366.1
AUSC (0 to 36) of SSS	68.0 ± 20.4	64.5 ± 23.7

Values are means ± SD.
*$P < 0.01$, compared with placebo.
AUSC indicates area under the score-time curve; $t_{1/2}$, half-life.

DISCUSSION

Because of its enormous popularity, caffeine intake is generally thought to be safe, and may be disregarded as a medical problem.[10] However, the reports on inhibition of clozapine metabolism by caffeine[11–13] indicate that this is not the case. In schizophrenic patients, caffeine withdrawal from the diet decreased plasma concentrations of clozapine by 47%.[12] In a healthy volunteer study,[13] caffeine increased the AUC of clozapine 19%. To study the interactions between caffeine and psychotropic drugs is important, because excessive caffeine intake is more prevalent in psychiatric patients than in the general population.[10] It was known that FLV inhibits the metabolism of caffeine,[22] but no study has examined the effect of caffeine on FLV metabolism.

In studying the effects of caffeine on drug metabolism, not only inhibition but also induction of CYP1A2 by caffeine should be considered. There have been several reports suggesting that caffeine intake induces CYP1A2 activity.[23,24] It has been estimated that consumption of 1 L of coffee containing about 440 mg of caffeine increases CYP1A2 activity 1.45-fold.[24]

In the present study, caffeine treatment significantly decreased the AUC of FLV 24%. Meanwhile, caffeine did not change the C_{max} or elimination $t_{1/2}$ of FLV. However, caffeine significantly reduced the plasma concentrations of FLV at several time points including 6 hours, which was close to the T_{max}. FLV has a high hepatic extraction ratio.[3] Induction of metabolism of a drug with a high hepatic extraction ratio reduces the C_{max} and AUC, but not elimination of $t_{1/2}$.[25] Therefore, the present results are almost in accordance with this pharmacokinetic principle, and suggest that caffeine slightly induces the metabolism of FLV. This induction is probably mediated by CYP1A2, because this enzyme is involved in FLV metabolism[5,6,8] and inducible by caffeine intake.[23,24] The specific metabolic pathway(s) of FLV induced by caffeine remains unclear, but the demethylation to FLA does not seem to be involved, because the pharmacokinetic parameters of FLA including the AUC-ratio of FLA to FLV were not significantly different between the 2 phases. Incidentally, no significant effect of caffeine on the demethylation of FLV accords well with the previous suggestion that this metabolic pathway is catalyzed mainly by CYP2D6.[26,27]

The slight to moderate inhibition of clozapine metabolism by caffeine in previous studies[12,13] is in contrast with the slight induction of FLV metabolism by caffeine in this study. This discrepancy does not seem to be ascribable to the doses of caffeine because, for instance, the doses were between 150 and 200 mg/d, which were even lower than those in this study, in the majority of patients in the study by Carrillo et al.[12] The more plausible explanation is the difference in the affinity for

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CYP1A2 between clozapine and FLV. The inhibition of clozapine metabolism by FLV reported in the literature[28] suggests a lower affinity of clozapine than FLV for CYP1A2. That is, during caffeine intake, CYP1A2 is induced and the metabolism of CYP1A2 substrates tends to be enhanced. However, clozapine has a relatively low affinity for CYP1A2, and metabolic inhibition by caffeine outweighs the metabolic induction that may occur.

Caffeine treatment induced no significant change in the pharmacodynamic effects of FLV. Some side effects of FLV, for example, palpitation and tremor,[1,2] overlap with those of caffeine.[10] Therefore, it is possible that the pharmacodynamic consequence of decreased FLV concentrations was nullified by that of induced caffeine concentrations caused by FLV.[22]

Finally, there were 2 drawbacks in this study. Firstly, caffeine treatment for 11 days might be too short to produce full inductions CYP1A2. The elimination $t_{1/2}$ of caffeine is relatively short, for example, 3 to 6 hours,[10] but it is likely that CYP1A2 induction by caffeine is based on increased protein synthesis[29] and, therefore, occurs with some delay. By the same token, the prohibition of caffeine intake for 1 week before the study might not have been sufficient to produce deinduction of CYP1A2. Secondly, caffeine concentrations were not measured when FLV was administrated. Because of this, unintentional caffeine intake in the placebo phase could not be checked, and the relationship between caffeine concentrations and the extent of induction of FLV metabolism in the caffeine phase could not be analyzed.

In conclusion, the present study suggests that caffeine slightly induces the metabolism of FLV, probably mediated by CYP1A2. As far as the authors know, this is the first demonstration of induction of drug metabolism by caffeine.

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