Effect of Venlafaxine on CYP1A2-Dependent Pharmacokinetics and Metabolism of Caffeine

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Venlafaxine is a clinically effective antidepressant. Caffeine is a metabolic probe for the quantitative measurement of CYP1A2 activity in vivo. This open-label study evaluated the effect of steady-state venlafaxine on CYP1A2-dependent metabolism, as measured by the pharmacokinetic disposition of caffeine, and urinary caffeine metabolite ratios (CMRs). Sixteen healthy subjects received 200 mg of caffeine orally before (Day 1) and after (Day 8) venlafaxine was titrated to steady-state (37.5 mg every 12 hours on Days 2-4, then 75 mg every 12 hours on Days 5-8). Samples were collected before and for 24 hours after caffeine dosing for the determination of caffeine in plasma and 1,7-dimethylxanthine, 3,7-dimethylxanthine, 1,7-dimethyluric acid (17U), 1-methylxanthine (1X) and 1-methyluric acid (1U), and 5-acetylamino-6-amino-3-methyluracil (AAMU) in urine. Blood samples were obtained before venlafaxine doses on Days 7 and 8 (morning dose only) for the determination of trough venlafaxine and O-desmethylvenlafaxine levels. Venlafaxine did not significantly alter the pharmacokinetics of caffeine and its metabolites. Plasma caffeine AUC was unchanged and remained within the bioequivalence criteria (90% confidence interval: 87.9%-102%) in the presence of venlafaxine. Urine metabolite data showed variable increases and decreases in the CMR [(AAMU + 1U + 1X)/17U] for individual subjects. However, the mean CMR was altered by < 10% in the presence of venlafaxine. This in vivo study demonstrated that venlafaxine did not alter the pharmacokinetic profile of caffeine and confirms in vitro data that venlafaxine does not inhibit CYP1A2 metabolism. Therefore, venlafaxine appears to have a relatively low potential for drug interactions based on CYP1A2 inhibition.

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INTRODUCTION

Attention has recently been focused on the potential for antidepressants to inhibit cytochrome P450 (cyp) isoenzymes. This study examined the effect of the antidepressant, venlafaxine, on CYP1A2. Venlafaxine is a structurally novel antidepressant; it is chemically unrelated to other antidepressants. Venlafaxine inhibits the neuronal reuptake of norepinephrine, serotonin, and, to a minor degree, dopamine, with little or no anticholinergic, antihistaminergic, or α-adrenergic activity.[1-4] The major metabolite of venlafaxine, O-desmethyl- venlafaxine, exerts pharmacologic activity similar to the parent compound.[5-7]

The pharmacokinetics of venlafaxine have been extensively studied and reviewed.[8-10] After oral administration, venlafaxine is well absorbed and undergoes extensive first-pass metabolism.[5,10] Approximately 80% of an oral dose of venlafaxine is recovered in the urine as the following: unchanged drug (5%), O-desmethylvenlafaxine (56%), and two minor inactive metabolites, N-desmethylvenlafaxine (1%) and N,O-didesmethylvenlafaxine (16%).[11] In vitro studies have shown that the O-demethylation

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metabolic pathway of venlafaxine is mediated primarily by CYP2D6, and the N-demethylation pathway is mediated by CYP3A4.[12,13] However, a drug may inhibit the activity of a specific isoenzyme even though it is not a substrate at that particular site. In vitro and/or in vivo data indicate that venlafaxine either does not significantly inhibit or weakly inhibits the activity of isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.[14-18]

Caffeine is useful as an in vivo metabolic probe due to its ubiquitous and safe consumption, rapid and complete gastrointestinal absorption, distribution throughout total body water, low plasma binding, short elimination half-life (mean = 5.4 hours), negligible first-pass metabolism, and biotransformation virtually confined to the liver.[19,20] The major enzyme involved in the N-demethylation of caffeine and its metabolites is CYP1A2.[21] Systemic caffeine clearance serves as a standard measure of in vivo CYP1A2 activity in most individuals since more than 95% of the systemic clearance of caffeine is estimated to be due to CYP1A2.[22] In humans, 3-demethylation of caffeine (1,3,7-trimethylxanthine) to paraxanthine (1,7-dimethylxanthine; 17X) is the most prominent reaction in the metabolism of caffeine, accounting for approximately 84% of caffeine demethylations. The 1-demethylated product (theobromine) and 7-demethylated product (theophylline) account for only 12% and 4%, respectively.[22,23] Paraxanthine's subsequent urinary products—1-methylxanthine (1X), 1-methyluric acid (1U), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and 1,7-dimethyluric acid (17U)—account for 30% to 55% of the administered dose of caffeine 24 hours after ingestion.[24,25] The unstable AFMU is deformylated to the stable 5-acetylamino-6-amino-3-methyluracil (AAMU) for quantitation.[26] The urinary caffeine metabolite ratio (CMR) of paraxanthine 7-demethylation products (AAMU + 1U + 1X) to the paraxanthine 8-hydroxylation product (17U) has been shown to reflect systemic caffeine clearance.[24,27]

Drug-drug interactions have been reported between the antidepressant fluvoxamine and CYP1A2 substrates, including caffeine,[28] theophylline,[29] clozapine,[30] imipramine,[29] and propranolol.[29] Fluvoxamine has been shown to be a potent inhibitor of CYP1A2 in vitro.[31] The disposition of fluvoxamine is mediated by both CYP1A2 and CYP2D6 activity.[32]

In vitro data have demonstrated that venlafaxine does not inhibit CYP1A2, as evidenced by IC_{50} values of > 1000 μM.[14] However, in vivo interaction studies with venlafaxine and CYP1A2 substrates are lacking. The purpose of this study was to further evaluate the in vivo effect of venlafaxine on CYP1A2-dependent metabolism, as measured by the pharmacokinetic disposition of caffeine and urinary CMRs.

SUBJECTS AND METHODS

Sixteen healthy volunteers (nine males and seven females) were enrolled in this study, which was conducted at the Pharmaceutical Product Development—Clinical Research Unit (Morrisville, NC). The study protocol was approved by the Western Institutional Review Board (Olympia, WA), and subjects signed informed consent. Mean (range) age, weight, and height for the subjects were 31.1 years (21 to 41 years), 70.5 kg (47 to 93 kg), and 172 cm (157 to 183 cm), respectively. Screening of subjects, within 2 weeks of study initiation, consisted of a medical history; physical examination, including a 12-lead electrocardiogram (ECG); clinical laboratory tests; urinary drug screen; vital signs; ethanol breath test; and serum pregnancy test (females only). Exclusion criteria included women of childbearing potential or use of tobacco products within 6 months, prescription drugs within 14 days, nonprescription drugs within 7 days, or investigational drugs or drugs known to induce or inhibit hepatic enzymes within 30 days of study drug administration. Subjects who routinely consumed more than five 8-ounce cups of coffee (or caffeine equivalent) per day were excluded from the study. Caffeine and xanthene-containing beverages and foods, as well as charcoal-grilled foods, were strictly prohibited from the evening of Day –2 through the morning of Day 9. Alcohol was prohibited from 7 days prior to the study and throughout the study.

Study Design

This was an open-label, nonrandomized drug interaction study to evaluate the effect of steady-state venlafaxine on CYP1A2-dependent metabolism, as measured by the pharmacokinetic disposition of caffeine and urinary CMRs. Eligible subjects were admitted to the clinic on Day 2 and remained there through Day 2. Subjects returned to the clinic as outpatients on Day 5, were readmitted on Day 6, and remained at the clinic through Day 9.

Caffeine (200 mg NoDoz® caplets, Bristol-Myers Products, New York, NY) was administered in single doses of 200 mg on Days 1 and 8. Caffeine doses were administered with 180 mL of room-temperature water at approximately 8 a.m., following an overnight fast. Venlafaxine (37.5 mg and 75 mg Effexor® tablets, Wyeth-Ayerst Laboratories, Philadelphia, PA) was

administered in multiple doses of 37.5 mg every 12 hours from Days 2 through 4 and then increased to 75 mg every 12 hours from Days 5 through 8. Venlafaxine doses were administered with 180 mL of room-temperature water at approximately 8 a.m. and 8 p.m. with food (except during the designated fasting period on Day 8, when it was administered without food).

The single-dose pharmacokinetic profile and urinary metabolite profile of caffeine were evaluated on Days 1 through 2 (caffeine alone) and on Days 8 through 9 (caffeine with venlafaxine). Safety assessments were based on reports of study events (adverse events) and results of routine physical examinations, laboratory determinations, and 12-lead ECGs evaluated throughout the study and prior to study discharge.

Pharmacokinetic Sampling

For the analysis of trough venlafaxine and O-desmethylvenlafaxine plasma concentrations, 10 mL blood samples were collected in heparinized Vacutainer® tubes immediately prior to each dose of venlafaxine on Day 7 and prior to the morning dose on Day 8. For the analysis of caffeine plasma concentrations, 10 mL blood samples were collected in heparinized Vacutainer® tubes on Days 1 and 8 at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after caffeine dosing. Urine samples were collected and pooled on Days 1 and 8 at the following times: predose and 0-4, 4-8, 8-12, and 12-24 hours following the caffeine dose.

Blood samples were centrifuged at 2500 rpm for 10 minutes at 4°C, and plasma was immediately stored in polypropylene screw-top tubes at –20°C or less until analysis. Urine volumes were measured, and three 20 mL aliquots were stored in polypropylene screw-top tubes and frozen at –20°C or less until analysis.

Analytical Methods

Assays of caffeine in plasma and caffeine metabolites in urine were processed using a validated analytical method with liquid-liquid extraction followed by reverse-phase high-performance liquid chromatography (HPLC) analysis at Wisconsin Analytical and Research Services, a division of PPD-CRU, Inc. (Madison, WI). Urine was analyzed for caffeine metabolites: 1X, 17X, 17U, 1U, and AAMU and 3,7-dimethylxanthine (37X). The determinations of these caffeine metabolites in urine were sensitive over an appropriate range of concentrations. The determination of caffeine concentrations in plasma was sensitive over the range of 0.1 to 10.0 µg/mL, with a limit of quantitation of 0.10 µg/mL. Quality control samples (containing 0.4 µg/mL, 4.0 µg/mL, and 8.0 µg/mL of caffeine) analyzed during sample processing had an interassay precision of 4.3% or less, with accuracy ranging from 85% to 102%.

Venlafaxine and O-desmethylvenlafaxine concentrations in plasma were measured at Bioassay Laboratory, Inc. (Houston, TX) using a validated method with liquid-liquid extraction followed by reverse-phase HPLC analysis with ultraviolet (UV) detection. The method was sensitive over the range of 5.0 to 500 ng/mL for the determination of venlafaxine and O-desmethylvenlafaxine plasma concentrations using a 1.0 mL sample. For quality control samples, interday precision was 5.7% and 6.0% or less for O-desmethylvenlafaxine and venlafaxine, respectively, and accuracy ranged from 99.2% to 111% and 95.2% to 106% for O-desmethylvenlafaxine and venlafaxine, respectively.

Pharmacokinetic Analysis

Single-dose pharmacokinetic parameters of caffeine were calculated by standard noncompartmental methods.[33] The maximum observed concentration and the corresponding sampling time were defined as C_{max} and t_{max}, respectively. The elimination rate constant (Ke) was determined from the slope of the regression line that best fit the terminal portion of the log-linear concentration-time curve. The terminal half-life, $t_{1/2}$, was calculated as 0.693/Ke. The area under the concentration-time curve up to the last sampling time, $AUC_{(0-t)}$, was calculated by the log-trapezoidal rule. The total area under the curve extrapolated to infinity, $AUC_{(0-inf)}$, was determined by summing $AUC_{(0-t)} + C_t/Ke$, where C_t was the last observed concentration. Apparent oral clearance (CL/F) of caffeine was calculated as dose/$AUC_{(0-inf)}$, and the apparent volume of distribution (Vd/F) was calculated as (CL/F)/Ke.

The cumulative amounts of caffeine and its metabolites excreted in urine over 24 hours were determined by summing the amounts excreted during each collection interval. The CYP1A2-dependent demethylation metabolite ratios were calculated from the cumulative 24-hour metabolites for each subject by taking the ratio of (AAMU + 1X + 1U)/17U.

Statistical Analysis

The SAS statistical software package[34] was used to calculate summary statistics and for statistical analyses. Results were considered statistically significant at $p < .05$.

The maximum percent difference among the three trough concentrations of venlafaxine and O-desmethylvenlafaxine was calculated for each subject by $[(Trough_{max} - Trough_{min})/Trough_{min}] \times 100$. In addition, regression analyses were conducted on each compound to determine steady state.

The variances of all pharmacokinetic parameters of caffeine were inspected to (1) verify they met the assumption of normality and (2) to detect potential outliers using diagnostic analysis (SAS, UNIVARIATE). Normality was determined by visual inspection of the normal curves and the Q-Q plots. The Shapiro-Wilks test statistic was also used as a quantitative measure of normality.[35] Values for $AUC_{(0-t)}$ and CMR that were two or more standard deviations from the mean were considered to be outliers and were further explored before actions were taken to omit them from the analysis.

When assumptions of normality were not met, the pharmacokinetic parameters were transformed to the natural log scale, and diagnostic analyses were again performed to determine the success of the transformation.[35] All parameters were analyzed by analysis of variance (ANOVA) using the general linear model procedure in SAS, except in those cases in which the assumptions of normality could not be satisfied by log transformation; in such cases, the nonparametric Wilcoxon rank sum test was used.

Bioequivalence was determined using the Schuirmann's two one-sided test procedure and the classical 90% confidence interval approach. Confidence limits were calculated on the basis of the least square means and the mean square error obtained from the ANOVA. The ± 20% decision rule was used in determining bioequivalence.[36]

RESULTS

Subjects

Fifteen of the 16 enrolled subjects completed the study. One subject withdrew consent and discontinued study participation on Day 5; thus, data from this subject were not included in the analysis. All subjects had normal baseline clinical laboratory profiles and physical examination findings. None of the subjects had any known illness at baseline that might have interfered with the pharmacokinetics of the study drugs or interpretation of the results.

Adverse Effects

All adverse events were considered by the investigator to be mild or moderate in intensity. No subject experienced a serious adverse event during this study.

Pharmacokinetic Results

Venlafaxine and O-desmethylvenlafaxine concentrations. Mean trough plasma concentrations of venlafaxine and O-desmethylvenlafaxine on Days 7 and 8 did not appear to change over time. Regression analysis showed that the slopes were not significantly different from zero for venlafaxine (slope = –0.697, p = .6311) and O-desmethylvenlafaxine (slope = –0.350, p = .8588), indicating that steady state had been attained for both compounds prior to concomitant administration with caffeine. Individual plasma venlafaxine concentrations did not show a bimodal distribution and ranged from 20 to 217 ng/mL. Nine of the 15 subjects had venlafaxine trough concentrations within the range of 15 to 70 ng/mL. The maximum percent difference between the three trough concentrations was calculated and found to be less than or equal to 30% for 10 of 15 subjects. For the remaining 5 subjects, the maximum percent difference between trough concentrations ranged from 31% to 49%. Individual trough plasma concentrations of O-desmethylvenlafaxine ranged from 56.0 to 338 ng/mL. The maximum percent difference between the three trough values was less than or equal to 25% for all subjects.

Caffeine pharmacokinetics. Mean plasma concentration versus time profiles of caffeine alone and with concomitant venlafaxine are illustrated in Figure 1. The pharmacokinetic parameter estimates for caffeine with and without venlafaxine coadministration are summarized in Table I. A wide range of caffeine half-life values was observed in this study (2.8 to 16 hours on Day 1 and 2.8 to 14.8 hours on Day 8). There was also a nearly sixfold range in caffeine clearance values (range: 27.1 mL/min to 153 mL/min) observed (42% and 44% coefficient of variation on Days 1 and 8, respectively).

The treatments did not differ significantly with respect to caffeine $AUC_{(0-inf)}$ and C_{max}, and both parameters remained within the bioequivalence 90% confidence interval criteria (87.9% to 102% for $AUC_{(0-inf)}$ and 99.4% to 117% for C_{max}). Venlafaxine coadministration also did not significantly alter caffeine t_{max}, CL/F, or Vd/F. A small (10%) but statistically significant decrease in caffeine half-life (6.10 ± 3.55 hours vs. 5.46 ± 3.19 hours) was observed in the presence of venlafaxine.

Urinary caffeine metabolites. The mean cumulative 24-hour urinary excretion of caffeine metabolites 17X, 37X, 17U, 1X, 1U, and AAMU, with and without venlafaxine coadministration, are summarized in Table II.

Table I Mean (± *SD*) Caffeine 200 mg Single-Dose Pharmacokinetic Parameters

Parameters	Caffeine (Day 1)	Caffeine + Venlafaxine (Day 8)	*p*-Value[a]	Geometric Mean Ratio (%)	90% Confidence Interval
$AUC_{(0-inf)}$ (µg • h/mL)	48.7 ± 26.9	46.4 ± 26.5	0.3535	94.7	87.9-102
C_{max} (µg/mL)	4.96 ± 0.83	5.48 ± 1.63	0.0814	108	99.4-117
t_{max} (h)	1.20 ± 0.68	1.00 ± 0.42	0.4554	—	—
$t_{1/2}$ (h)	6.10 ± 3.55	5.46 ± 3.19	0.0125	—	—
CL/F (mL/min)	84.8 ± 35.5	90.3 ± 40.1	0.1776	—	—
Vd/F (L)	36.7 ± 8.1	35.0 ± 8.1	0.1040	—	—

n = 15 subjects. *SD*, standard deviation; $AUC_{(0-inf)}$, area under the curve extrapolated to infinity; C_{max}, maximum observed concentration; t_{max}, sampling time corresponding to C_{max}; $t_{1/2}$, terminal half-life; CL/F, apparent oral clearance of caffeine; Vd/F, apparent volume of distribution.
a. *p*-values, using arithmetic means, are from ANOVA associated with treatment differences for all parameters except t_{max}, which is from the Wilcoxon rank sum test.

Table II Mean (± *SD*) Cumulative 24-Hour Urinary Excretion of Caffeine Metabolites

Urinary Analyte (mg)	Caffeine (Day 1)	Caffeine + Venlafaxine (Day 8)
17X	8.75 ± 3.07	7.96 ± 2.75
37X	1.91 ± 0.94	1.66 ± 0.48
17U	13.4 ± 3.6	13.7 ± 4.4
1X	15.2 ± 5.9	16.7 ± 6.3
1U	24.5 ± 9.0	25.7 ± 8.7
AAMU	36.1 ± 18.6	39.6 ± 21.2

n = 16 subjects for Day 1 and n = 15 subjects for Day 8. 17X = 1,7-dimethylxanthine; 37X = 3,7-dimethylxanthine; 17U = 1,7-dimethyluric acid; 1X = 1-methylxanthine; 1U = 1-methyluric acid; and AAMU = 5-acetylamino-6-amino-3-methyluracil. No statistically significant differences ($p > 0.05$) in metabolic urinary excretion between treatments using ANOVA.

There were no statistically significant differences in the excretion of caffeine metabolites between treatments.

The CYP1A2 demethylation metabolite ratios are presented for each subject and as mean values in Table III. Ten subjects had an increase in the CMR on Day 8 (caffeine + venlafaxine) as compared with Day 1 (caffeine alone). A decrease in the metabolite ratio on Day 8 was observed in five subjects. With the exception of two subjects (both males), the percent change in the metabolite ratios was essentially ± 25% or less. One subject had a 44% decrease and another subject had a 49% increase in the metabolite ratio from Day 1 to Day 8. The mean urinary CMR was altered by less than 10% in the presence of venlafaxine and was not statistically different between treatments. The metabolite ratios were not statistically different between male and female subjects, and there was no apparent difference in the response to the addition of venlafaxine.

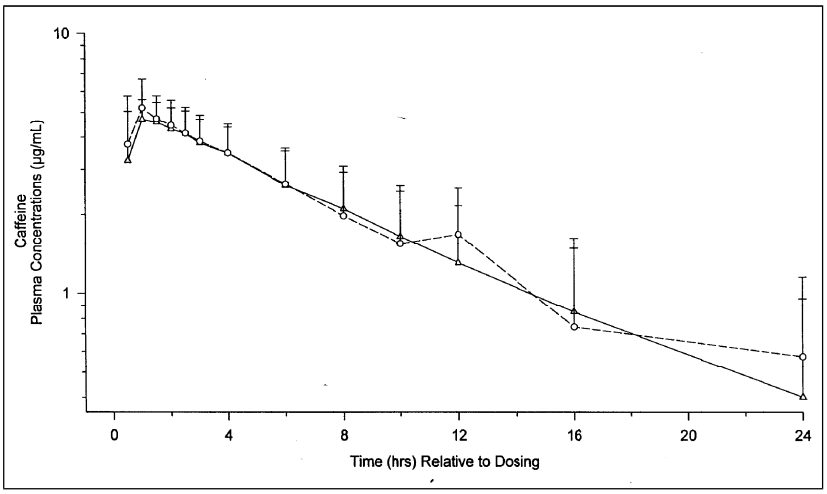

*Figure 1. Mean (*SD*) plasma concentrations of caffeine following single-dose administration of caffeine with (open circles) and without (triangles) coadministration of multiple-dose venlafaxine.*

Table III Caffeine Metabolite Ratios (CMR)[a] by Subject

Subject Number	Gender	Caffeine (Day 1)	Caffeine + Venlafaxine (Day 8)	% Change[b]
001	Female	8.96	10.6	18.3
002	Male	7.72	7.78	0.777
003	Male	10.0	5.63	–43.7
004	Male	5.05	4.11	–18.6
005	Female	5.03	4.93	–1.99
006	Male	6.29	9.36	48.8
007	Male	2.65	3.42	29.1
008	Female	6.01	8.09	34.6
009	Male	4.33	5.08	17.3
010	Female	3.37	3.72	10.4
011	Male	4.37	5.53	26.5
012	Female	4.84	—[c]	—[c]
013	Female	5.16	5.28	2.33
014	Male	6.60	8.34	26.4
015	Male	8.86	8.02	–9.48
016	Female	3.80	3.58	–5.79
Mean ± *SD*	All subjects	5.82 ± 2.13	6.23 ± 2.29	9.00 ± 23.5
	Males	6.21 ± 2.37	6.36 ± 2.07	8.57 ± 28.7
	Females	5.31 ± 1.83	6.03 ± 2.77	9.64 ± 15.0

No statistically significant differences ($p > 0.05$) in CMR between treatments or between males and females using ANOVA.

a. Caffeine metabolite ratio is defined as (AAMU + 1X + lU)/17U, where AAMU = 5-acetylamino-6-amino-3-methyluracil; 1X = 1-methylxanthine; 1U = 1-methyluric acid; 17U = 1,7-dimethyluric acid.

b. % change = (Day 8 CMR – Day 1 CMR)/(Day 1 CMR) × 100, where CMR = caffeine metabolite ratio.

c. Subject discontinued study prior to Day 8; no data available.

DISCUSSION

The purpose of this study was to explore a potential drug interaction between venlafaxine and caffeine, a drug biotransformed by the P450 isoenzyme CYP1A2. The study was designed to evaluate the effects of venlafaxine, administered under steady-state conditions at 75 mg every 12 hours, on the pharmacokinetic profile of a single oral 200 mg dose of caffeine. This study also evaluated the in vivo effect of venlafaxine on CYP1A2 metabolic activity.

The doses of venlafaxine, caffeine, and their combination used in this study were generally well tolerated.

Steady-state venlafaxine and O-desmethylvenlafaxine levels were attained following venlafaxine multiple doses of 37.5 mg twice daily for 3 days followed by 75 mg twice daily for 4 days. Mean plasma concentrations of venlafaxine and O-desmethyl- venlafaxine were within the range reported by Troy et al[8] for subjects given a 75 mg twice-daily regimen of venlafaxine for 3 or more days. These represent typical doses of venlafaxine used in depressed patients.

The pharmacokinetic parameters obtained for caffeine administered alone in this study (Table I) were similar to those reported previously in normal subjects.[19,24] The caffeine dose administered in this study approximated the amount in three cups of coffee per day. Caffeine doses greater than 300 mg (> four cups of coffee) per day are not recommended to avoid possible saturation kinetics, which have been observed at doses of 3 mg/kg/day to 12 mg/kg/day,[24] and caffeine doses of 12 mg/kg/day have been shown to invalidate use of the CMR to assess CYP1A2 activity.[22]

Venlafaxine did not significantly alter the pharmacokinetic profile of caffeine. Specifically, there was a lack of significant alteration in the total clearance of caffeine, assuming no change in the bioavailability of caffeine between doses. Therefore, on the basis of this study, it appears that caffeine may be safely coadministered with venlafaxine.

Wide interindividual and intraindividual variability in CYP1A2 activity has been reported.[29] This is evident in the almost sixfold range in caffeine clearance values in this study. CYP1A2 activity is known to be

affected by inducers (i.e., cigarette smoke, consumption of charcoal-broiled beef, and polycyclic aromatic hydrocarbons) and inhibitors (i.e., oral contraceptives, furafylline, and fluvoxamine), but it is not believed to be under genetic polymorphic control.[37] Reportedly, males have higher CMR values than females, and Caucasians have higher CMR values than Asian subjects.[38,39] Age also appears to affect CYP1A2 activity, with children between 3 and 11 years of age exhibiting CMR values as high as some cigarette smokers.[39] Male and female subjects (who were not taking oral contraceptives) in this study had similar CMR values and showed a similar response to the addition of venlafaxine. This is in agreement with the findings of Kalow and Tang,[26] who showed that when the use of oral contraceptives was accounted for, there was no significant difference between the sexes with respect to the CYP1A2 index.

Urinary metabolite data showed variable increases and decreases in the calculated metabolite ratio for individual subjects. Since a wide range of caffeine half-life values was observed, this variability could be due to incomplete urine collections with longer caffeine elimination half-lives in some subjects. In this study, recovery of subsequent urinary products of 1,7-dimethylxanthine (1X, 1U, AAMU, and 17U) accounted for 46% of the administered caffeine dose, which is in agreement with the 30% to 55% recovery of these metabolites reported in the literature.[25] Collections of urine over shorter periods or even spot urine collections have been shown to reliably estimate CMR. Since the metabolite ratios relate the amounts of metabolites to one another, they are essentially independent of total recovery from urine.[25] The mean urinary CMR was altered by less than 10% with the coadministration of venlafaxine. Therefore, venlafaxine did not appreciably alter the CYP1A2-mediated metabolism of caffeine, as measured by the CMR as well.

In conclusion, this study demonstrated that the presence of venlafaxine, administered under steady-state conditions at 75 mg twice daily, did not significantly alter the pharmacokinetic profile of a single 200 mg dose of caffeine. Analysis of major caffeine metabolites revealed slight variations in CMRs for individual subjects. However, venlafaxine did not appreciably alter the overall CYP1A2-mediated CMR. This in vivo study showed that venlafaxine did not alter the pharmacokinetic profile of caffeine and confirms in vitro data that venlafaxine does not inhibit CYP1A2 metabolism. Therefore, venlafaxine appears to have a low potential for drug interactions based on CYP1A2 inhibition.

REFERENCES

1. Richelson E: Pharmacology of antidepressants: characteristics of the ideal drug. *Mayo Clin Proc* 1994;69:1069-1081.

2. Scott MA, Shelton PS, Gattis W: Therapeutic options for treating major depression and the role of venlafaxine. *Pharmacotherapy* 1996;16:352-365.

3. Cohen LJ: Rational drug use in the treatment of depression. *Pharmacotherapy* 1997;17:45-61.

4. Montgomery SA: Venlafaxine: a new dimension in antidepressant pharmacotherapy. *J Clin Psychiatry* 1993;54:119-126.

5. Klamerus KJ, Maloney D, Rudolph RL, Sisenwine SF, Jusko WJ, Chiang ST: Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active O-desmethyl metabolite. *J Clin Pharmacol* 1992;32:716-724.

6. Muth EA, Moyer JA, Haskins JT, Andree TH, Husbands GEM: Biochemical, neurophysiological and behavioral effects of Wy-45,233, its enantiomers and other identified metabolites of the antidepressant venlafaxine. *Drug Dev Res* 1991;23:191-199.

7. Muth EA, Moyer JA, Andree TH: A pharmacological profile of Wy-45,233, the major metabolite in humans of the novel bicyclic antidepressant candidate, Wy-45,030 (abstract). *Soc Neurosci* 1986;12:473.

8. Troy SM, Parker VD, Fruncillo RJ, Chiang ST: The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995;35:404-409.

9. Troy SM, Schultz RW, Parker VD, Chiang ST, Blum RA: The effect of renal disease on the disposition of venlafaxine. *Clin Pharmacol Ther* 1994;56:14-21.

10. Holliday SM, Benfield P: Venlafaxine: a review of its pharmacology and therapeutic potential in depression. *Drugs* 1995;49:280-294.

11. Howell SR, Husbands GEM, Scatina JA, Sisenwine SF: Metabolic disposition of ^{14}C-venlafaxine in mouse, rat, dog, rhesus monkey and man. *Xenobiotica* 1993;23:349-359.

12. Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, Sellers EM: Venlafaxine oxidation in vitro is catalysed by CYP2D6. *Br J Clin Pharmacol* 1996;41:149-156.

13. Fogelman S, Schmider J, Greenblatt DJ, Shader RI: Metabolism of venlafaxine: the role of P450 isoforms (abstract). *J Clin Pharmacol* 1995;35:936.

14. Ball SE, Ahern D, Scatina J, Kao J: Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism: comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol* 1997;43:619-626.

15. Ereshefsky L: Drug-drug interactions involving antidepressants: focus on venlafaxine. *J Clin Psychopharmacol* 1996;16(Suppl. 2):37S-53S.

16. Amchin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM: Effect of venlafaxine on the pharmacokinetics of terfenadine. *Psychopharmacol Bull* 1998;34(3):383-389.

17. Amchin J, Ereshefsky L, Zarycranski WM: Effect of venlafaxine versus fluoxetine on the metabolism of dextromethorphan, a CYP2D6 marker. Presented at the 149th annual meeting of the American Psychiatric Association, May 1996, New York.

18. von Moltke LL, Duan SX, Greenblatt DJ, Fogelman SM, Schmider J, Harmatz JS, Shader RI: Venlafaxine and metabolites are very weak inhibitors of human cytochrome P450-3A isoforms. *Biol Psychiatry* 1997;41:377-380.

19. Tang-Liu DD-S, Williams RL, Riegelman S: Disposition of caffeine and its metabolites in man. *J Pharmacol Exp Ther* 1983;224:180-185.

20. Benowitz NL: Clinical pharmacology of caffeine. *Ann Rev Med* 1990;41:277-288.

21. Tassaneeyakul W, Birkett DJ, McManus ME, Tassaneeyakul W, Veronese ME, Andersson T, et al: Caffeine metabolism by human hepatic cytochromes P450: contributions of 1A2, 2E1 and 3A isoforms. *Biochem Pharmacol* 1994;47:1767-1776.

22. Kalow W, Tang B-K: The use of caffeine for enzyme assays: a critical appraisal. *Clin Pharmacol Ther* 1993;53:503-514.

23. Lelo A, Miners JO, Robson RA, Birkett DJ: Quantitative assessment of caffeine partial clearances in man. *Br J Clin Pharmacol* 1986;22:183-186.

24. Campbell ME, Spielberg SP, Kalow W: A urinary metabolite ratio that reflects systemic caffeine clearance. *Clin Pharmacol Ther* 1987;42:157-165.

25. Grant DM, Tang BK, Kalow W: Variability in caffeine metabolism. *Clin Pharmacol Ther* 1983;33:591-602.

26. Kalow W, Tang B-K: Use of caffeine metabolite ratios to explore CYP1A2 and xanthine oxidase activities. *Clin Pharmacol Ther* 1991;50:508-519.

27. Denaro CP, Wilson M, Jacob P III, Benowitz NL: Validation of urine caffeine metabolite ratios with use of stable isotope-labeled caffeine clearance. *Clin Pharmacol Ther* 1996;59:284-296.

28. Jeppesen U, Loft S, Poulsen HE, Brøsen K: A fluvoxamine-caffeine interaction study. *Pharmacogenetics* 1996;6:213-222.

29. Brøsen K: Drug interactions and the cytochrome P450 system: the role of cytochrome P450 1A2. *Clin Pharmacokinet* 1995;29:20-25.

30. Jerling M, Lindström 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.

31. Rasmussen BB, Mäenpää J, Pelkonen O, Loft S, Poulsen HE, Lykkesfeldt J, Brøsen K: Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995;39:151-159.

32. Carrillo JA, Dahl ML, Svensson JO, Alm C, Rodriguez I, Bertilsson L: Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin Pharmacol Ther* 1996;60:183-190.

33. Jusko WJ: Guidelines for collection and analysis of pharmacokinetic data. In, Evans WE, Schentag JJ, Jusko WJ (eds.): *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. 3rd ed. Vancouver: Applied Therapeutics, 1992;2-1–2-43.

34. SAS Institute, Inc: *SAS/STAT User's Guide*. Version 6, 4th ed., vols. 1 and 2. Cary, NC: SAS Institute, Inc., 1990.

35. Steel RGD, Torrie JH: *Principles and Procedures of Statistics*. New York: McGraw-Hill, 1980.

36. Chow SC, Liu JP: Recent statistical developments in bioequivalence trials: a review of the FDA guidance. *Drug Information Journal* 1994;28:851-864.

37. Sesardic D, Boobis AR, Edwards RJ, Davies DS: A form of cytochrome P450 in man, orthologous to form d in the rat, catalyses the o-deethylation of phesacetin and is inducible by cigarette smoking. *Br J Clin Pharmacol* 1988;26:363-372.

38. Carrillo JA, Benitez J: CYP1A2 activity, gender and smoking, as variables influencing the toxicity of caffeine. *Br J Clin Pharmacol* 1996;41:605-608.

39. Tang B-K, Kalow W: Assays for CYP1A2 by testing in vivo metabolism of caffeine in humans. In, Johnson EF, Waterman MR (eds.): *Methods in Enzymology*. New York: Academic Press, 1996;124-131.