Fluvoxamine drastically increases concentrations and effects of tizanidine: A potentially hazardous interaction

Objective: **Our objective was to study the effect of fluvoxamine on the pharmacokinetics and pharmacodynamics of tizanidine, a centrally acting skeletal muscle relaxant.**

Methods: **In a double-blind, randomized, 2-phase crossover study, 10 healthy volunteers took 100 mg fluvoxamine or placebo orally once daily for 4 days. On day 4, each ingested a single 4-mg dose of tizanidine. Plasma concentrations of tizanidine and fluvoxamine and pharmacodynamic variables were measured. A caffeine test was performed on day 3 to examine the role of cytochrome P450 (CYP) 1A2 in tizanidine pharmacokinetics.**

Results: **On average, fluvoxamine increased the total area under the concentration-time curve [AUC(0-∞)] of tizanidine 33-fold (range, 14-fold to 103-fold; $P = .000002$) and the peak plasma concentration 12-fold (range, 5-fold to 32-fold; $P = .000001$). The mean elimination half-life of tizanidine was prolonged from 1.5 to 4.3 hours ($P = .00004$) by fluvoxamine. The AUC(0-∞) of tizanidine and its increase by fluvoxamine correlated with the caffeine/paraxanthine ratio and its increase, respectively ($P < .03$). All pharmacodynamic variables revealed a significant difference between the fluvoxamine and placebo phases, eg, in the maximal effects on systolic blood pressure (−35 mm Hg, $P = .000009$), diastolic blood pressure (−20 mm Hg, $P = .00002$), heart rate (−4 beats/min, $P = .007$), Digit Symbol Substitution Test ($P = .0003$), subjective drug effect ($P = .0000001$), and drowsiness ($P = .0002$). In particular, the decrease in systolic blood pressure, to the level of 80 mm Hg or even less, was an alarming finding.**

Conclusions: **Fluvoxamine seriously affects the pharmacokinetics of tizanidine and increases the intensity and duration of its effects. Inhibition of tizanidine-metabolizing enzyme(s), mainly CYP1A2, by fluvoxamine seems to explain the observed interaction. Because of the potentially hazardous consequences, the concomitant use of tizanidine with fluvoxamine, or other potent inhibitors of CYP1A2, should be avoided. (Clin Pharmacol Ther 2004;75:331-41.)**

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Tizanidine is a centrally acting skeletal muscle relaxant that has been in clinical use for about 20 years. It is generally used for the symptomatic treatment of acute painful muscle spasms and chronic spasticity resulting from diverse neurologic disorders.[1,2] Tizanidine seems to have several pharmacologic effects, but its mechanism of action is not clearly defined. The antispasticity effects of tizanidine are thought to be mediated by its α_2-adrenergic agonistic properties.[1-3] The oral bioavailability of tizanidine is low, about 20% on average, and it is eliminated mainly by metabolism.[2,4] However, there are no previously published data on the enzymes responsible for its biotransformation. We have recently observed that cytochrome P450 (CYP) 1A2 is in vitro the principal CYP enzyme involved in the elimination of parent tizanidine.[5]

Fluvoxamine, a selective serotonin reuptake inhibitor antidepressant, is a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP3A4,

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Table I. Characteristics of subjects

	Age (y)	*Weight (kg)*	*Fluvoxamine AUC(0-25) (ng · h/mL)*	*Fluvoxamine C_{max} (mg/L)*	*Caffeine/paraxanthine ratio*	
					During placebo (control)	*During fluvoxamine*
Subject No.						
1	23	68	1681	81	2.16	52.40
2	23	65	1127	57	1.01	10.43
3	23	83	962	79	1.79	16.64
4	23	80	1594	121	0.92	10.56
5	31	80	1197	66	1.49	11.41
6	24	76	1390	71	2.75	18.64
7	22	72	721	43	3.24	32.17
8	22	72	1007	53	0.90	23.54
9	26	73	1059	58	1.16	10.46
10	21	75	1253	93	2.37	37.22
Mean±SD	24 ± 3	75 ± 5	1199 ± 293	72 ± 23	1.78 ± 0.83	22.35 ± 14.18*

AUC(0-25), Area under plasma concentration–time curve; C_{max}, maximum plasma concentration.
*P = .002, versus control.

CYP2C9, and CYP2D6.[6-9] In humans, fluvoxamine considerably increases the plasma concentrations of CYP1A2 substrate drugs, such as ropivacaine, caffeine, theophylline, clozapine, and tacrine.[9-13] Antidepressants and muscle relaxants are fairly commonly used to treat chronic pain syndromes (eg, fibromyalgia). Thus it is conceivable that fluvoxamine and tizanidine can be coadministered in this kind of clinical situation. As the estimated 50% inhibitory concentration (IC_{50}) value (0.7 μmol/L) of fluvoxamine for the in vitro metabolism of 80-nmol/L tizanidine (Granfors MT, Backman JT, Neuvonen PJ, unpublished data) is close to the therapeutic plasma concentration of fluvoxamine, we found it important to investigate the effects of fluvoxamine on the pharmacokinetics and pharmacodynamics of tizanidine in healthy volunteers.

METHODS

Subjects. Ten healthy male volunteers (age range, 21-31 years; weight range, 65-83 kg) participated in the study after giving written informed consent (Table I). Male subjects were chosen to avoid possible effects of menstrual cycle phases on tizanidine pharmacokinetics. The volunteers were ascertained to be healthy by medical history, physical examination, and routine laboratory tests before entering the study. For safety reasons, subjects with a systolic blood pressure lower than 110 mm Hg were excluded from the study. None of the subjects were tobacco smokers, and none used any continuous medication.

Study design. The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects of the Hospital District of Helsinki and Uusimaa and the Finnish National Agency for Medicines. A double-blind, randomized, 2-phase crossover study with a washout period of 4 weeks was carried out. The volunteers received 100 mg fluvoxamine (two 50-mg capsules of Fevarin; Solvay Pharmaceuticals BV, Weesp, Holland) or matched placebo once daily at 8:00 AM for 4 days. On day 4, after an overnight fast, a single oral dose of 4 mg tizanidine (one 4-mg tablet of Sirdalud; Novartis, Espoo, Finland) was administered with 150 mL water at 9 AM. A standard meal was served 4 and 7 hours after tizanidine administration. Drinking of grapefruit juice and tobacco smoking were not allowed for 1 week before the study. Alcohol and drinks containing caffeine were not permitted on the study days.

To evaluate the possible association between CYP1A2 activity in vivo and tizanidine pharmacokinetics, a caffeine test was performed on the third day of the pretreatment during both phases.[14-16] The subjects ingested 100 mg caffeine (one 100-mg Cofi-Tabs tablet; Vitabalans, Hämeenlinna, Finland) at 9 AM, after having abstained from caffeine intake for at least 12 hours, and a blood sample for analysis of plasma caffeine and paraxanthine (1,7-dimethylxanthine) was taken from each subject 6 hours after caffeine intake.

The subjects were under direct, close medical supervision during the days of tizanidine administration. Fluids for intravenous infusion were available for immediate use, but they were not needed.

Sampling. On the days of tizanidine administration, a forearm vein in each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples were drawn before the adminis-

tration of tizanidine and at 20, 40, 60, and 90 minutes and 2, 3, 4, 5, 7, 9, 12, and 24 hours later. Blood samples (10 mL each) were taken into ethylenediaminetetraacetic acid–containing tubes. Plasma was separated within 30 minutes and stored at −40°C until analysis. Urine was collected cumulatively in 2 fractions, 0 to 12 hours and 12 to 24 hours.

Determination of plasma drug concentrations. Plasma tizanidine concentrations were quantified by liquid chromatography–tandem mass spectrometry with use of the Perkin-Elmer SCIEX API 3000 LC/MS/MS System (Sciex Division of MDS Inc, Toronto, Ontario, Canada). A Zorbax SB-CN column (150 × 2.1 mm; Agilent Technologies, Wilmington, Del) and a mobile phase consisting of acetonitrile (60%), 10-mmol/L ammonium acetate (pH 5.0; adjusted with glacial acetic acid, 20%), and 2-propanol (20%) were used. The mass spectrometer was operated in the turbo ion spray mode with positive ion detection, and plasma tizanidine was measured by the Q1 single ion monitoring method by use of the mass-to-charge ratio (*m/z*) value 254. This *m/z* value represents the $[M+H]^+$ ion for tizanidine. The limit of quantification was 0.04 ng/mL, and the day-to-day coefficient of variation (CV) was 12.6% at 0.1 ng/mL and 9.4% at 1.0 ng/mL (n = 5). Fluvoxamine did not interfere with the determination of plasma tizanidine.

The plasma concentrations of fluvoxamine were determined by HPLC.[17] The limit of quantification was 10 ng/mL, and the day-to-day CV values were 4.2% at 18 ng/mL and 3.9% at 320 ng/mL (n = 4).

Plasma caffeine and paraxanthine concentrations were determined by HPLC with ultraviolet detection, with β-hydroxy-ethyltheophylline used as the internal standard.[18,19] The day-to-day CV of caffeine and paraxanthine was less than 3% at relevant concentrations.

Pharmacokinetics. The pharmacokinetics of tizanidine was characterized by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration–time curve (AUC) from time 0 to infinity [AUC(0-∞)], and elimination half-life ($t_{½}$). The terminal log-linear part of the concentration-time curve was visually identified for each subject. The elimination rate constant (k_e) was determined with the use of linear regression analysis of the log-linear part of the plasma concentration–time curve. The $t_{½}$ was calculated by the following equation:

$$t_{½} = \ln 2/k_e$$

The AUC values were calculated by use of the linear trapezoidal rule for the rising phase of the plasma tizanidine concentration–time curve and the log-linear trapezoidal rule for the descending phase, with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. The pharmacokinetic parameters of fluvoxamine were characterized by C_{max} and the AUC from 0 to 25 hours after the last dose of fluvoxamine [AUC(0-25)]. The pharmacokinetic calculations were performed with the program MK-model, version 5.0 (Biosoft, Cambridge, United Kingdom).

Pharmacodynamics. The pharmacodynamic variables were assessed before administration of tizanidine and immediately after each blood sampling, up to 24 hours. The systolic and diastolic blood pressures and heart rate were measured twice from the forearm with the subject in a sitting position, and the mean value was used in the calculations. The blood pressures and heart rates were measured with an automatic oscillometric blood pressure monitor (HEM-711; Omron Healthcare GmbH, Hamburg, Germany). Before the study started, the volunteers were trained properly to perform 3 psychomotor tests.[7,20,21] In the Digit Symbol Substitution Test (DSST), the number of digits correctly substituted in 2 minutes was recorded. Subjective drowsiness and subjective overall drug effect were measured with a 100-mm-long horizontal visual analog scale. For each pharmacodynamic variable, the area under the effect versus time curve from 0 to 12 hours [AUC(0-12)] was calculated by use of the trapezoidal rule. In addition, the maximum responses in each pharmacodynamic variable were recorded.

Statistical analysis. Results are expressed as mean ± SD. The pharmacokinetic and pharmacodynamic variables after the 2 pretreatments were compared by repeated-measures ANOVA with treatment sequence as a factor or, in the case of t_{max}, with the Wilcoxon signed-rank test. For all variables except t_{max}, 95% confidence intervals were calculated on the mean differences between the placebo and fluvoxamine phases. The Pearson correlation coefficient was used to investigate possible relationships between the pharmacokinetic variables or plasma concentrations of tizanidine and the following variables: the plasma caffeine/paraxanthine concentration ratio, the pharmacodynamic variables measured, and the pharmacokinetic variables of fluvoxamine. All data were analyzed with the statistical program Systat for Windows, version 6.0.1 (SPSS Inc, Chicago, Ill). The differences were considered statistically significant at $P < .05$.

RESULTS

Pharmacokinetics of tizanidine. Fluvoxamine drastically increased the plasma concentrations of tizanidine (Table II, Fig 1). Fluvoxamine increased the mean

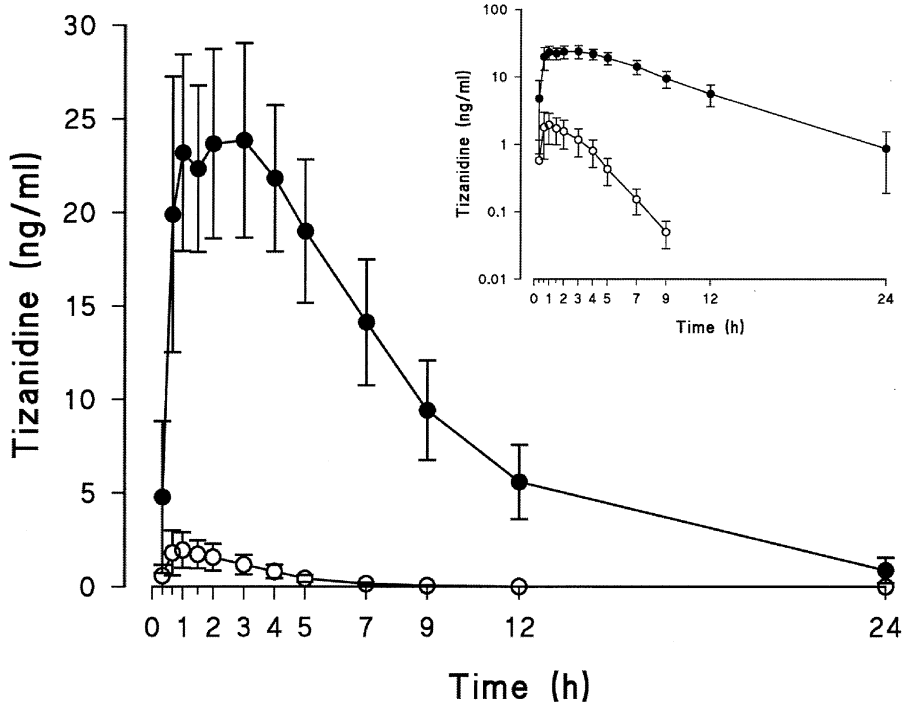

Fig 1. Mean ± SD plasma concentrations of tizanidine in 10 healthy volunteers after single oral dose of 4 mg tizanidine after treatment with placebo or 100 mg fluvoxamine once daily for 4 days. *Open circles*, Tizanidine during placebo; *solid circles*, tizanidine during fluvoxamine. *Inset* depicts the same data on a semilogarithmic scale. Time 0 refers to administration of tizanidine (ie, 1 hour after the last dose of fluvoxamine).

Table II. Pharmacokinetic variables of 4 mg tizanidine in 10 healthy volunteers after 4-day pretreatment with 100 mg fluvoxamine or placebo

Variable	*Placebo phase (control)*	*Fluvoxamine phase*	*Difference between phases*	*P value*
C_{max} (ng/mL)	2.2 ± 0.9	26.6 ± 5.6	24.4 (19.9-28.8)	.000001
% of control and range	100	1210 (540-3210)		
t_{max} (min)	60 (40-120)	90 (40-240)		.17
t½ (h)	1.5 ± 0.1	4.3 ± 1.1	2.8 (2.0-3.6)	.00004
% of control and range	100	290 (190-430)		
AUC(0-∞) (ng · h/mL)	6.6 ± 2.9	216.0 ± 51.6	209.3 (169.2-249.4)	.000002
% of control and range	100	3260 (1370-10350)		

Data are mean ± SD or mean with 95% CI; percentage of control is given with range; t_{max} data are given as median with range.
CI, Confidence interval; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life; AUC(0-∞), area under plasma concentration–time curve from time 0 to infinity.

AUC(0-∞) of tizanidine to 3260% (P = .000002) and the C_{max} to 1210% (P = .000001) of that during placebo. The mean elimination t½ of tizanidine was prolonged almost 3-fold, from 1.5 to 4.3 hours (P = .00004), by fluvoxamine. Substantial increases in the C_{max} (range, 5-fold to 32-fold), t½ (range, 2-fold to 4-fold), and total AUC (range, 14-fold to 103-fold) values were seen in every subject (Fig 2, *A-C*). The relative increase in the AUC(0-∞) of tizanidine by fluvoxamine correlated inversely with the AUC(0-∞) values of tizanidine in the placebo phase (r = −0.78, P = .008) (Fig 2, *D*).

Pharmacodynamic variables. The pharmacodynamic responses to tizanidine were much stronger during the fluvoxamine phase than during the placebo phase (Table III, Fig 3). There were great differences

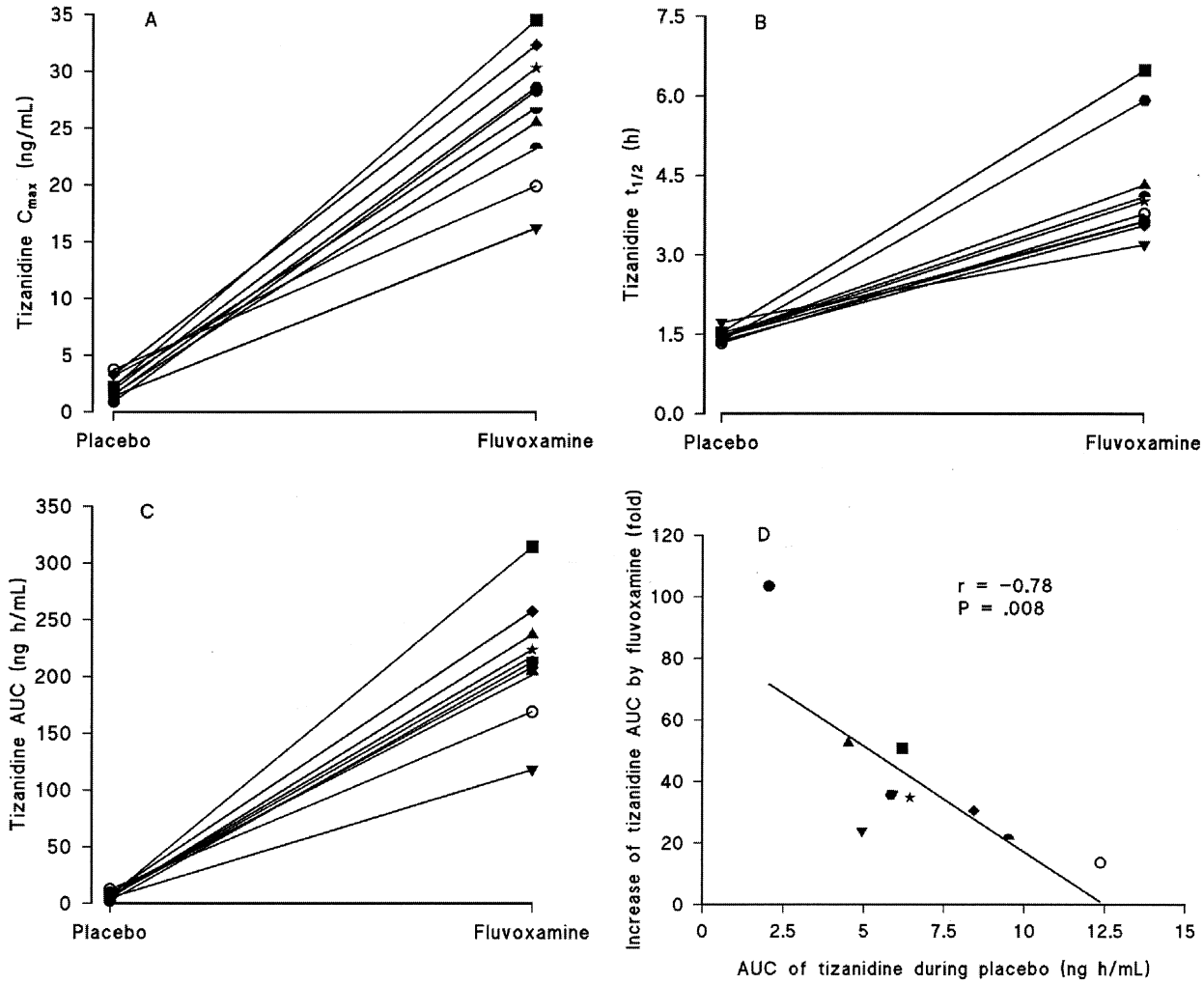

Fig 2. Individual values for peak concentration in plasma (C_{max}) (**A**), elimination half-life ($t_{½}$) (**B**), and area under plasma concentration–time curve from time 0 to infinity [AUC(0-∞)] (**C**) of tizanidine in 10 healthy volunteers after single oral dose of 4 mg tizanidine after treatment with placebo or 100 mg fluvoxamine once daily for 4 days. **D**, Relationship between the AUC(0-∞) of tizanidine during the placebo phase and the relative increase in the AUC(0-∞) of tizanidine by fluvoxamine.

between the phases in the maximal effects on systolic blood pressure (−35 mm Hg, $P = .000009$), diastolic blood pressure (−20 mm Hg, $P = .00002$), heart rate (−4 beats/min, $P = .007$), subjective drowsiness ($P = .0002$) and drug effect ($P = .0000001$), and DSST ($P = .0003$). During the fluvoxamine phase, the mean values (±SD) of the lowest systolic and diastolic blood pressure were 79 ± 10 mm Hg and 46 ± 5 mm Hg, respectively, which are significantly less than the corresponding pressures during the placebo phase (115 ± 8 mm Hg [$P = .000009$] and 66 ± 7 mm Hg [$P = .00002$], respectively). During the fluvoxamine phase, the lowest heart rate (48 ± 6 beats/min) was significantly less than during the placebo phase (52 ± 5 beats/min, $P = .007$).

There were significant correlations ($P < .0000001$) between the plasma concentration of tizanidine and the change from baseline value in systolic blood pressure ($r = −0.84$), diastolic blood pressure ($r = −0.76$), heart rate ($r = −0.34$), subjective drowsiness ($r = 0.64$) and drug effect ($r = 0.84$), and DSST ($r = −0.76$) (Fig 4).

Table III. Maximum effects of tizanidine (minimum or maximum) and AUC(0-12) for systolic and diastolic blood pressure, heart rate, and psychomotor tests (subjective drowsiness [VAS], subjective drug effect [VAS], and digit symbol substitution test [DSST]) after a single oral 4-mg dose of tizanidine given after pretreatment with oral fluvoxamine (100 mg) or placebo daily for 4 days in 10 healthy volunteers

Variable	*Placebo phase (control)*	*Fluvoxamine phase*	*Difference between phases*	*P value*
Systolic blood pressure				
Min. (mm Hg)	115 ± 8	79 ± 10	35 (27-44)	.000009
AUC(0-12) (mm Hg · h)	1553 ± 94	1163 ± 106	360 (278-441)	.000008
Diastolic blood pressure				
Min. (mm Hg)	66 ± 7	46 ± 5	20 (15-25)	.00002
AUC(0-12) (mm Hg · h)	882 ± 72	666 ± 65	219 (184-254)	.0000005
Heart rate				
Min. (beats/min)	52 ± 5	48 ± 6	4 (2-7)	.007
AUC(0-12) (beats/min · h)	735 ± 80	652 ± 79	83 (31-134)	.006
VAS: Drowsiness				
Max. (mm)	52 ± 20	94 ± 7	42 (27-57)	.0002
AUC(0-12) (mm · h)	348 ± 160	607 ± 144	259 (194-324)	.00002
VAS: Drug effect				
Max. (mm)	9 ± 5	85 ± 12	76 (66-85)	.0000001
AUC(0-12) (mm · h)	24 ± 23	397 ± 152	373 (262-484)	.00006
DSST				
Min. (symbols/2 min)	92 ± 9	63 ± 12	29 (18-40)	.0003
AUC(0-12) (symbols/2 min · h)	1179 ± 115	1028 ± 97	150 (86-215)	.0006

Data are mean ± SD or mean with 95% CI.
AUC(0-12), Area under effect versus time curve from time 0 to 12 hours; Min., minimum; VAS, visual analog scale; Max., maximum; DSST, Digit Symbol Substitution Test.

Fluvoxamine concentrations. The AUC(0-25) and C_{max} of fluvoxamine varied 2.3- and 2.8-fold, respectively, between the individual subjects (Table I). There were significant correlations between the AUC(0-25) of fluvoxamine and the increases in the AUC(0-∞) (r = 0.64, P = .05) and C_{max} (r = 0.63, P = .05) of tizanidine (Fig 5).

Caffeine test. Fluvoxamine increased the plasma caffeine/paraxanthine concentration ratio 12.5-fold (P = .002) (Table I). The AUC(0-∞) of tizanidine and its increase by fluvoxamine correlated with the caffeine/paraxanthine ratio and its increase, respectively (P < .03) (Fig 6).

Adverse effects. During the fluvoxamine phase, all 10 subjects were somnolent and dizzy for 3 to 6 hours after tizanidine intake. They had difficulties in fixating the eyes and concentrating on the psychomotor tests. Muscle weakness and dry mouth were reported during the fluvoxamine phase. Despite grave hypotension, the heart rate was lowered and the extremities were warm. The adverse effects were much milder during the placebo phase.

During the fluvoxamine phase, the subjects did not void during the first 6 hours after tizanidine intake, even though the hypotensive subjects were encouraged to drink water. During the first 12 hours, the urine volume was 859 ± 364 mL in the fluvoxamine phase and 1098 ± 334 mL in the placebo phase (P = .004).

DISCUSSION

This study shows that fluvoxamine drastically affects the pharmacokinetics and pharmacodynamics of tizanidine. Fluvoxamine increased the AUC(0-∞) of tizanidine 33-fold; in some subjects, it increased the AUC(0-∞) much more, up to 103-fold. In addition, the C_{max} and $t_{½}$ of tizanidine were increased, on average, 12-fold and 3-fold, respectively.

During the fluvoxamine phase, administration of a usual therapeutic dose of 4 mg tizanidine resulted within 1 to 2 hours in severe systolic and diastolic hypotension, which lasted for 7 to 12 hours. This grave hypotension was accompanied by a decrease in heart rate, consistent with the α_2-adrenergic agonistic properties of tizanidine.[1-3] The volunteers were very somnolent and dizzy, and their psychomotor performance was reduced for about 7 to 9 hours after tizanidine administration during the fluvoxamine phase. These pharmacodynamic effects were noticed to a much milder extent during the placebo phase.

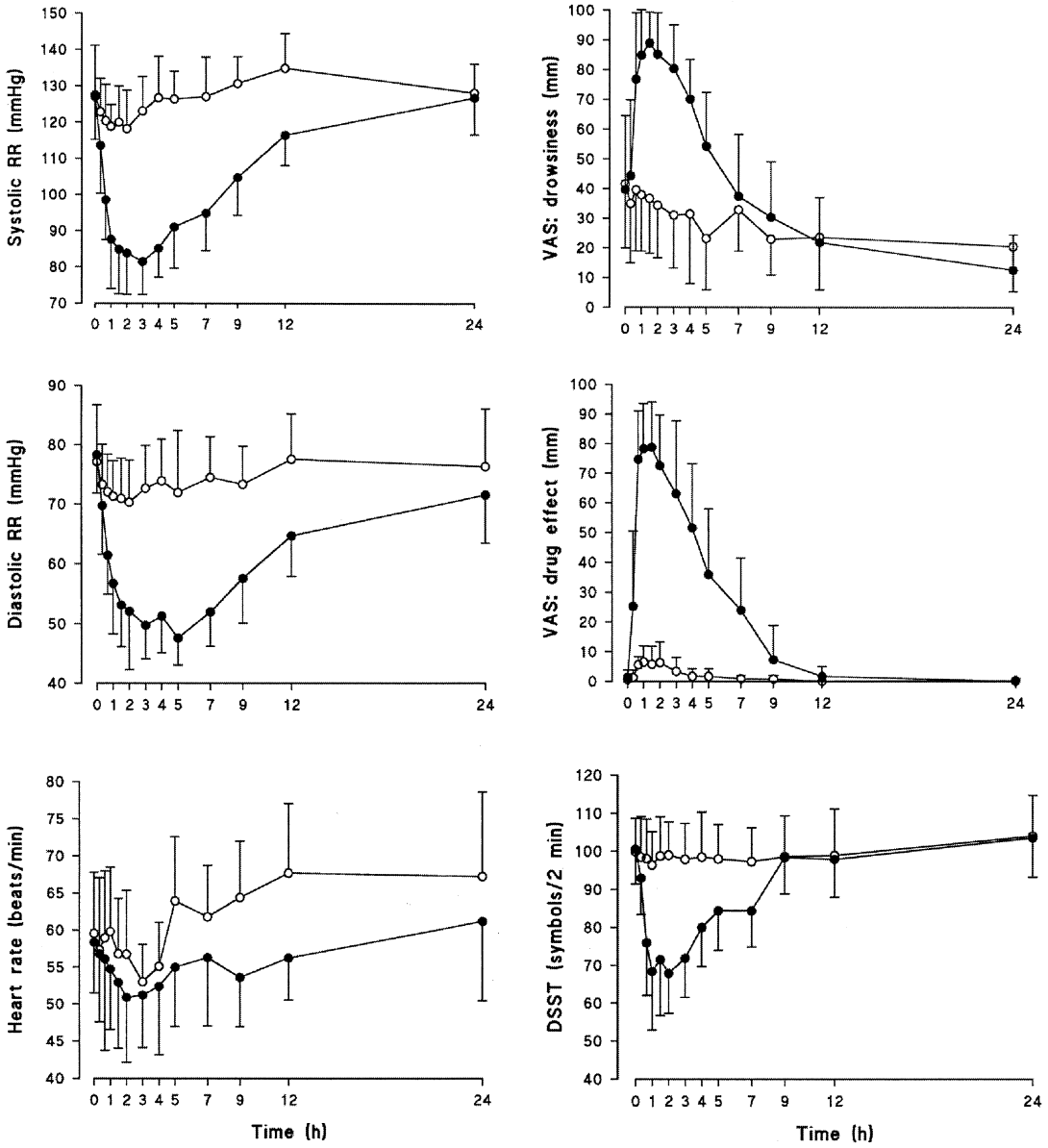

Fig 3. Mean ± SD systolic and diastolic blood pressure (RR) and heart rate values, recordings of subjective drowsiness and drug effect (visual analog scale [VAS]), and results of Digit Symbol Substitution Test (DSST) after 4-mg oral dose of tizanidine after pretreatment with placebo or 100 mg fluvoxamine once daily for 4 days. *Open circles*, Tizanidine during placebo; *solid circles*, tizanidine during fluvoxamine.

Premedication with fluvoxamine did not cause any changes in the pharmacodynamic variables measured, as judged from the similar baseline pharmacodynamic values during the placebo and fluvoxamine phases. Thus, although there was no fluvoxamine-only phase in this study, we believe that the pharmacodynamic effects observed during the fourth day, after the ingestion of tizanidine, were caused by tizanidine and not by fluvoxamine. This conclusion is further supported by the highly significant correlations between the plasma concentration of tizanidine and the changes from baseline in the pharmacodynamic variables (Fig 4).

Tizanidine undergoes a significant first-pass metabolism and has an oral bioavailability of approximately

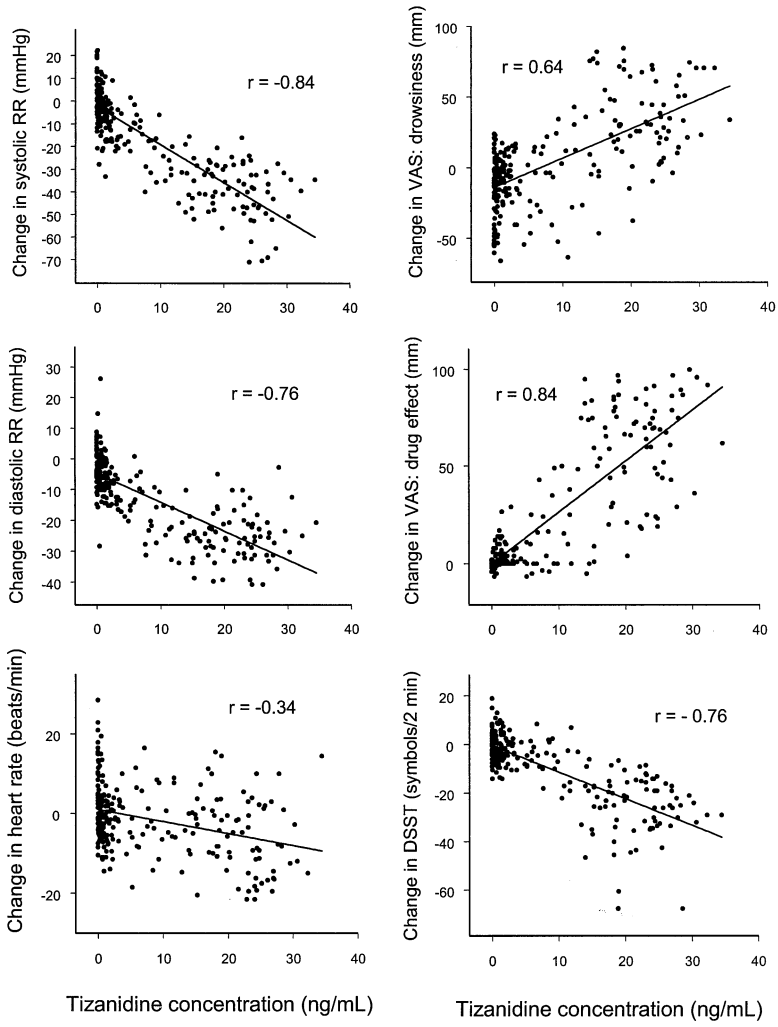

Fig 4. Relationship between plasma concentration of tizanidine and change from baseline in systolic and diastolic blood pressure and heart rate, subjective drowsiness and drug effect, and results of DSST during fluvoxamine and placebo phases ($P < .0000001$ in all cases).

20%.[2] Given that fluvoxamine markedly increased both the C_{max} and t½ of tizanidine, it seems that fluvoxamine inhibits the biotransformation of tizanidine during both the absorption and elimination phases; that is, it increases the oral bioavailability and decreases the plasma clearance of tizanidine.

Fluvoxamine is in vivo a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[6-9] Using human liver microsomes, chemical CYP isoform inhibitors, and complementary deoxyribonucleic acid–expressed (recombinant) human CYP isoforms, we recently found in vitro that tizanidine is metabolized primarily by CYP1A2.[5] Furthermore, fluvoxamine inhibits the metabolism of tizanidine (80 nmol/L [ie, about 20 ng/mL]) with an estimated IC_{50} of 0.7 μmol/L, which is close to the therapeutic plasma concentration of fluvoxamine. The results of this in vivo study fit well with the results obtained in vitro.

A caffeine test was included in this in vivo study to evaluate the possible association between the plasma caffeine/paraxanthine concentration ratio, a validated index of in vivo CYP1A2 activity,[15,16] and tizanidine pharmacokinetics. Significant correlations were found between the AUC(0-∞) of tizanidine and the caffeine test results, as well as their changes (Fig 6). This further supports the role of CYP1A2 in the metabolism of tizanidine and the inhibition of CYP1A2 by fluvoxam-

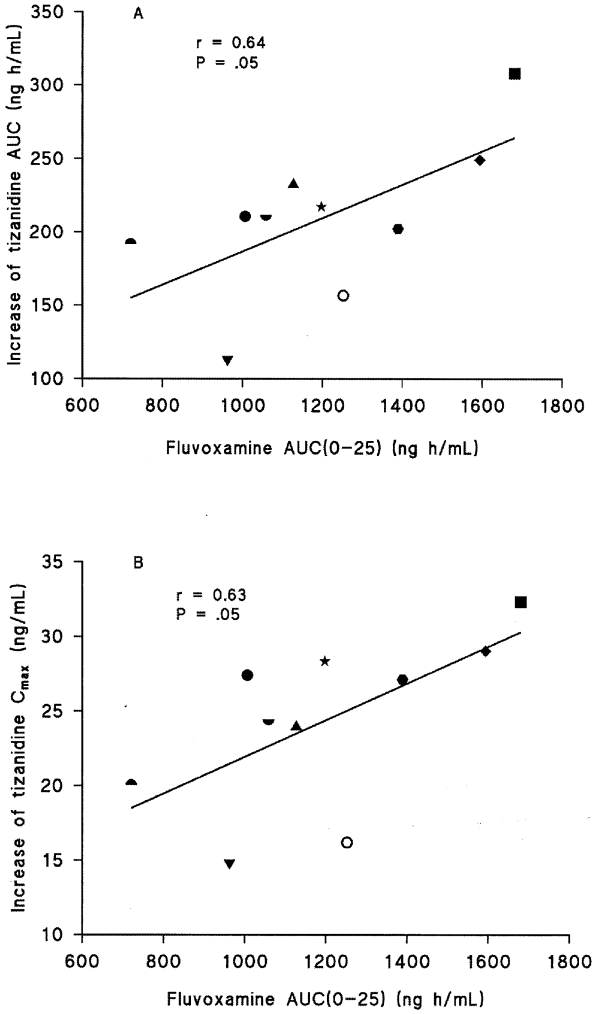

Fig 5. Relationship between AUC(0-25) of fluvoxamine and increase in AUC(0-∞) (**A**) and C_{max} (**B**) of tizanidine during fluvoxamine and placebo phases.

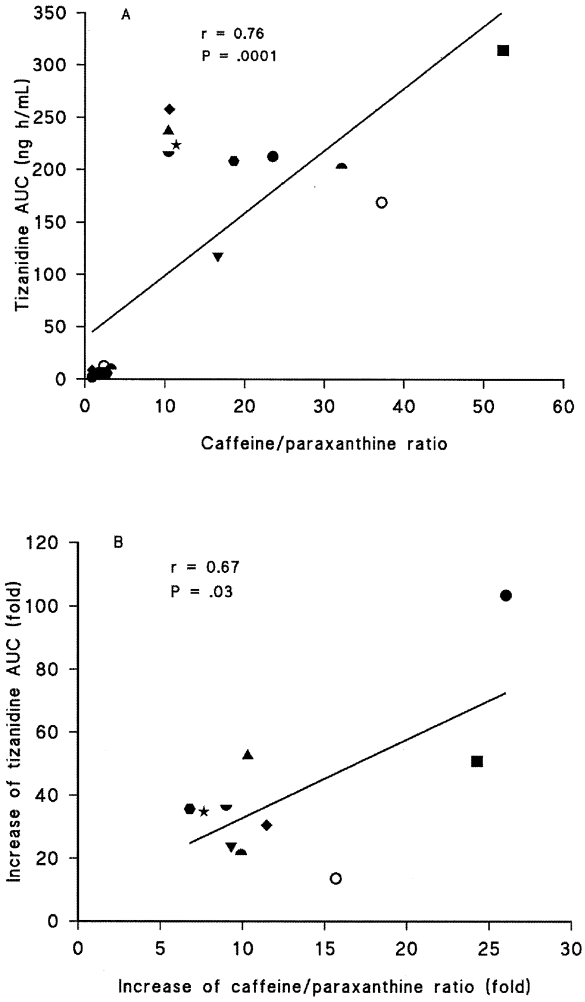

Fig 6. Relationship between AUC(0-∞) of tizanidine and caffeine/paraxanthine ratio during fluvoxamine and placebo phases (**A**) and between relative increases in AUC(0-∞) of tizanidine and in plasma caffeine/paraxanthine concentration ratio by fluvoxamine (**B**).

ine as the mechanism of the fluvoxamine-tizanidine interaction.

In previous reports fluvoxamine has been shown to increase the plasma concentrations of several drugs that are metabolized by CYP1A2. For example, 50-mg/d fluvoxamine raised the AUC(0-∞) of caffeine 5-fold,[10] 75-mg/d fluvoxamine raised the AUC(0-∞) of theophylline 2.4-fold,[11] and 100-mg/d fluvoxamine raised the AUC(0-∞) of clozapine 2.8-fold,[12] the AUC(0-∞) of ropivacaine 3.7-fold,[9] and the AUC(0-∞) of tacrine 8.3-fold.[13] The effect of fluvoxamine on the pharmacokinetics of tizanidine is thus by far the strongest drug-drug interaction reported for CYP1A2 substrates.

Even though large changes in tizanidine pharmacokinetics and pharmacodynamics by fluvoxamine could be seen in every subject, there were prominent variations between the individuals. For example, the AUC(0-∞) of tizanidine increased 103-fold in one subject but only 14-fold in another. The interindividual differences in the extent of the interaction can be explained by individual variations in the activity of CYP1A2; subjects with a high CYP1A2 activity have a small AUC(0-∞) of tizanidine in the placebo phase and, accordingly, a large increase in tizanidine AUC(0-∞) after fluvoxamine administration.

Both tizanidine and fluvoxamine are widely used drugs. For example, in Finland, the daily consumption of tizanidine was 1.75 defined daily doses (DDD)/1000

inhabitants (DDD for tizanidine is 12 mg/d) and that of fluvoxamine was 0.79 DDD/1000 inhabitants (DDD for fluvoxamine is 100 mg/d) during the year 2002.[22] Different types of acute and chronic pain syndromes are common in patients with depression or other indications for selective serotonin reuptake inhibitor antidepressants. Thus it is probable that in clinical practice both fluvoxamine and tizanidine can be coadministered even more frequently than expected on the basis of their average consumption.

The clinical significance of the fluvoxamine-tizanidine interaction is obvious. The therapeutic range of tizanidine seems to be narrow and the concentration-effect relationship rather steep (eg, regarding blood pressure and psychomotor function). It should be emphasized that the subjects in this study were healthy young men; it is possible that the effects in elderly and infirm individuals, for example, could be even greater. The severe hypotension observed can be hazardous to patients. In particular, elderly patients who have an increased risk of heart or brain ischemia must not use tizanidine and fluvoxamine concomitantly. Moreover, the greatly increased drowsiness can considerably impair psychomotor function and reduce the capability to perform tasks that require skills (eg, driving a car).

Fluvoxamine seems to be the most potent inhibitor of CYP1A2 among clinically used drugs.[23,24] However, there are also other generally used drugs and compounds that inhibit (eg, oral contraceptives, ciprofloxacin, rofecoxib)[23,25,26] or induce (eg, cigarette smoking, rifampin [INN, rifampicin])[25,27] the activity of human CYP1A2. Several cases of adverse effects (eg, hypotension, bradycardia, somnolence) have recently been reported during concomitant treatment with rofecoxib and tizanidine, but the mechanism of this possible drug-drug interaction has remained unclear.[28] Furthermore, women concurrently taking oral contraceptives have a 50% lower clearance of tizanidine than women not taking oral contraceptives, on the basis of retrospective analysis of population pharmacokinetic data.[28] Studies to resolve the effects of potential CYP1A2 inhibitors and inducers on the pharmacokinetics and pharmacodynamics of tizanidine are in progress in our laboratory.

In conclusion, fluvoxamine drastically raises the plasma concentrations of tizanidine by inhibiting its CYP1A2-mediated biotransformation. Clinicians should know that fluvoxamine may dangerously increase the concentration-dependent adverse effects of tizanidine; their concomitant use must be avoided. Care should also be exercised in the concomitant use of tizanidine and other inhibitors of CYP1A2.

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