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A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine

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Abstract. We have assesed the pharmacokinetic and pharmacodynamic interaction between fluvoxamine, a serotonin reuptake inhibitor, and alprazolam, a triazolobenzodiazepine.

Healthy men took fluvoxamine maleate daily for 10 days (50 mg on days 1–3, 100 mg on days 4–10) ($n = 20$), 1 mg of alprazolam four times daily for four days (days 7–10 of the study period) ($n = 20$), or a combination of the two ($n = 20$), according to a parallel study design. Alprazolam and fluvoxamine concentrations were measured in serial plasma samples by HPLC and gas chromatography respectively, and psychomotor performance and memory were assessed on days 1, 7, and 10.

Fluvoxamine increased plasma alprazolam concentrations by 100 %. The mean apparent half-life of alprazolam was increased from 20 h to 34 h after fluvoxamine co-administration.

The increased plasma concentrations of alprazolam resulted in significantly greater reductions in psychomotor performance evident on day 10. Mean fluvoxamine plasma concentrations were about 25 % lower in those who took the combination than in those who took only fluvoxamine; this was more likely due to heterogeneity between the treatment groups than to an effect of alprazolam.

The dosage of alprazolam should be reduced during co-administration with fluvoxamine.

Key words: Psychomotor performance, Fluvoxamine, Alprazolam; metabolic inhibition, sedation, drug interaction, serotonin reuptake inhibitor, benzodiazepine

Fluvoxamine is a serotonin reuptake inhibitor that has been used in the treatment of depression and obsessive-compulsive disorder. It is primarily cleared by hepatic metabolism to inactive metabolites, and it inhibits the metabolism of several other compounds, including warfarin, propranolol, and bromazepam, all of which are eliminated by metabolic oxidation [1, 2]. The pharmacokinetics of lorazepam, which is primarily eliminated by glucuronidation, were unaffected by fluvoxamine [2].

Patients with depression may also suffer from other psychiatric symptoms, such as anxiety and insomnia, and may require treatment in addition to antidepressants. In one study, 30 % of the subjects treated with fluvoxamine were also given benzodiazepines [1]. Alprazolam is a triazolobenzodiazepine used in the treatment of anxiety and panic disorder [3–5], and thus may be co-administered with fluvoxamine. It is eliminated in man by hepatic oxidation to the active metabolites α-hydroxyalprazolam and 4-droxyalprazolam, which are then glucuronidated [6].

We have therefore studied the pharmacokinetic and pharmacodynamic interaction between alprazolam and fluvoxamine during repeated dosing.

Materials and methods

This study was conducted at the Arkansas Research Medical Testing Center. The protocol was approved by the local Institutional Review Board, and each subject provided written informed consent before enrolment. We enrolled 60 men (30 smokers and 30 non-smokers), aged 20–44 years and weighing 59–100 kg.

The subjects were in good health, judging by physical examination and standard clinical laboratory tests. They took no enzyme-inducing drugs for 30 days and no medications at all for 7 days before the study started. During the study they took no medications other than those specified in the protocol. They also abstained from alcohol for 2 days before and on study days.

They were randomly assigned to one of three treatments: a) one 50 mg fluvoxamine maleate capsule at 08.00 h for 3 days and two 50 mg fluvoxamine maleate capsules at 08.00 h for the next 7 days, with one placebo tablet (matching alprazolam) at 08.00, 13.00, 18.00, and 23.00 h on study days 7–10; b) one placebo capsule at 08.00 h for 3 days and two placebo capsules at 08.00 h for 7 days, with one alprazolam 1.0 mg tablet at 08.00, 13.00, 18.00, and 23.00 h on study days 7–10; c) one 50 mg fluvoxamine maleate capsule at 08.00 h for 3 days and two 50 mg fluvoxamine maleate capsules at 08.00 h for 7 days, with one alprazolam 1.0 mg tablet at 08.00, 13.00, 18.00, and 23.00 h on study days 7–10. Smokers and nonsmokers were evenly distributed among the three treatment groups. The treatments were

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given double blind. The subjects remained in the clinic throughout the study period and ate standard meals at 07.00, 12.00, 18.00, and 22.00 h on all study days.

Venous blood samples (10 ml) for the determination of fluvoxamine were collected into heparinized tubes (Vacutainer®) at the following times: day 1 – before and at 1, 2, 4, 6, 8, 12, 16, and 20 h after fluvoxamine; days 2–9 – before the morning dose of fluvoxamine; day 10 – before and at 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 21, 24, 29, and 36 h after the last dose of fluvoxamine. Plasma was harvested from the samples after centrifugation and frozen until analysed. Determinations of fluvoxamine in plasma were made by capillary gas chromatography with electron-capture detection, using a modification of the method of Hurst et al. [7]. Standard curves for fluvoxamine concentrations were linear over the range 0.073–73.3 $ng \cdot ml^{-1}$. The coefficients of variation (CV) for the assay were 9.2% and 14.1% at 3.66 and 58.6 $ng \cdot ml^{-1}$, respectively; at 0.29 $ng \cdot ml^{-1}$, the CV was 33%.

Venous blood samples (5 ml) for the determination of alprazolam and metabolites were collected into heparinized tubes (Vacutainer®) at the following times: day 7 – before and at 1, 2, 4, 5, 6, 7, 9, 10, 11, 12, 14, 15, and 20 h after the 08.00 h dose of alprazolam; days 8–9 – before the morning dose of alprazolam; day 10 – before and at 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 21, 24, 29, and 36 h after the 08.00 h dose of alprazolam. Plasma was harvested and frozen until analysed. Determinations of alprazolam, α-hydroxyalprazolam, and 4-hydroxyalprazolam in plasma were made by HPLC [6]. Standard curves for alprazolam and its metabolites were linear over the concentration range 1–100 $ng \cdot ml^{-1}$. At a concentration of 3.0 $ng \cdot ml^{-1}$, CVs were 4.7%, 5.2%, and 6.5% for α-hydroxyalprazolam, 4-hydroxyalprazolam, and alprazolam respectively.

Non-compartmental techniques were used in the pharmacokinetic analyses [8]. Because the plasma concentrations of metabolites of alprazolam were low, their pharmacokinetic parameters were not calculated. The terminal elimination rate constant (λ_z) was determined by linear regression of the linear terminal portion of the log concentration-time profile. Half-life was calculated as $\ln 2/\lambda_z$ after the last dose on day 10. After the first dose of fluvoxamine, the area under the drug concentration-time curve was determined by the linear trapezoidal method to 24 hours ($AUC_{0\to24}$). After the first dose of alprazolam, $AUC_{0\to5}$ was calculated by the linear trapezoidal method. $AUC_{0\to24}$ for both drugs on day 10 was also evaluated by the linear trapezoidal method. Maximal plasma concentrations (C_{max}) and the times at which they occurred (t_{max}) were determined graphically. On day 10, the oral clearance (CL_{PO}) for alprazolam was calculated as the daily dose divided by the $AUC_{0\to24}$. The apparent volume of distribution (V_z/f) was calculated as CL_{PO}/λ_z. Neither value was calculated for fluvoxamine, because steady-state fluvoxamine pharmacokinetics are poorly predicted from single-dose kinetics [9].

Visual inspection of the alprazolam concentration-time curves showed that steady-state alprazolam concentrations were not achieved at day 10 in the subjects who took both fluvoxamine and alprazolam. Thus, values for alprazolam CL_{PO} and V_z/f for this treatment are overestimated using the above approach. In addition, the estimate of alprazolam half-life from both treatments was suspect, because of the limited sample collections after the last dose of alprazolam. In order to analyze these data more effectively, we used the following equation for a one-compartment model with first-order absorption and first order elimination

$$C = \frac{fDk_a}{V_z(k_a - \lambda_z)} \cdot (e^{-\lambda_z t} - e^{-k_a t}) \quad (1)$$

was fit to the alprazolam data for each treatment using the nonlinear regression routine NLIN in SAS [10]; because of the unequal dosing intervals, superposition was used to allow analysis of the data throughout the dosing period [8]. In other words, the data were modelled by overlaying the predicted concentration-time profiles of single 1 mg alprazolam doses (calculated from Equation 1) and summing the values to determine predicted concentrations at each time. The adequacy of the fits were judged by examining the residuals and the standard deviations of the parameter estimates for the individual fits. The parameters estimated were V_z/f, λ_z, and the absorption rate constant k_a. AUC (assuming single-dose administration) was calculated as:

$$AUC = \frac{A}{\lambda_z} - \frac{A}{k_a} \quad (2)$$

where A is the zero time intercept on the concentration axis, assuming no lag time. CL_{PO} and V_z/f were calculated as described previously, except that AUC was used in their calculation. The effects of treatment on pharmacokinetics were assessed using unpaired t-tests.

Psychomotor performance tasks consisted of the Symbol Digit Substitution (SDS), Continuous Performance (CPT), and Digit-Span (DS) modules of the NES2 computerized neurobehavioural computer battery (Neurobehavioral Systems, Inc.) [11]. SDS and CPT were used as measures of psychomotor performance, and DS was a measure of immediate recall. For the SDS, the subjects were asked to correctly substitute a series of digits for a series of symbols according to a key they were given. In the CPT, they were shown letters (A, S, and T) at 3-second intervals and were asked to respond every time an S appeared on the screen. In the digit-span test they were asked to remember successively longer strings of digits, shown one digit at a time. In the first part of the test they were asked to input the digits in the order shown; in the second part, they were asked to input the digits in the reverse order. The subjects practised all three tasks during three sessions on the evening before the first drug administration. Performance tests were administered before and at 2, 4, 6, and 10 h after the 08.00 h doses on days 1, 7, and 10. At these times sedation was also rated by an observer using the Nurse-Rated Sedation Scale [6, 12].

The measures of psychomotor performance obtained from the NES2 system were the mean response latency per digit on the SDS, the mean response latency on the CPT, the number of false positive responses on the CPT, the number of non-responses on the CPT, the number correctly recalled forwards on the DS, and the number correctly recalled backwards on the DS. The scores for these tests were analyzed by one-way analysis of covariance (ANCOVA) at each time the determinations were made. For the determinations on day 1, the covariate was the zero-hour determination on day 1. Since analysis of data from day 1 showed no effect of treatment on performance, the covariate for analysis of the scores on days 7 and 10 was the zero-hour score on day 7. Sedation scores were analyzed by ANOVA at each time.

Results

We studied 60 subjects, who completed all protocol activities. The sample size was chosen to provide a power of approximately 80% to detect a 30% difference in psychomotor performance at $\alpha = 0.05$. There were no significant

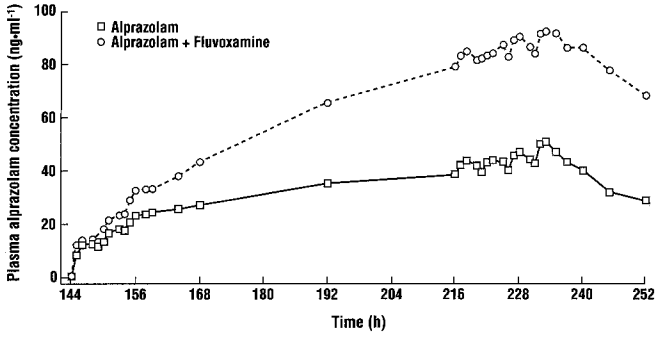

Fig. 1. Mean plasma concentrations of alprazolam after 4.0 mg/day alprazolam alone or 100 mg/day fluvoxamine maleate plus 4.0 mg/day alprazolam in healthy male volunteers

Table 1. Mean (SD) alprazolam pharmacokinetics determined by non-compartmental methods after alprazolam alone and alprazolam plus fluvoxamine

Parameter	Treatment	
	Alprazolam	Alprazolam + Fluvoxamine
	Day 1	
$AUC_{0\to5}$ ($ng \cdot h \cdot ml^{-1}$)	48.6* (9.90)	61.0* (9.86)
C_{max} ($ng \cdot ml^{-1}$)	13.0* (2.26)	15.3* (2.07)
t_{max} (h^{-1})	2.95 (1.36)	2.90 (1.51)
	Day 10	
$AUC_{0\to24}$ ($ng \cdot h \cdot ml^{-1}$)	1058* (224)	2077* (460)
CL_{PO} ($l \cdot h^{-1}$)	3.97* (0.96)	2.03* (0.513)
C_{max} ($ng \cdot ml^{-1}$)	53.6* (11.4)	99.8* (21.6)
t_{max} (h)	15.8 (5.64)	13.6 (5.89)
V_z/f (l)	121 (37.9)	118 (37.7)

* Significantly different by unpaired *t*-test at $P < 0.05$

Table 2. Mean (SD) alprazolam pharmacokinetics determined by non-linear least squares regression analysis following alprazolam alone and alprazolam plus fluvoxamine

Parameter	Treatment	
	Alprazolam	Alprazolam + fluvoxamine
AUC ($ng \cdot h \cdot ml^{-1}$)[a]	288* (72.5)	654* (201)
CL_{PO} ($l \cdot h^{-1}$)	3.72* (1.07)	1.67* (0.52)
λ_z (h^{-1})	0.041* (0.016)	0.023* (0.007)
$t_{1/2}$ (h)	19.8* (9.35)	33.9* (11.3)
V_z/f (l)	97.8* (27.5)	75.6* (15.0)

[a] From equation 2 and NLIN generated parameter estimates
* Signiicantly different by unpaired *t*-test at $P < 0.05$

differences in age or weight among the treatment groups. The treatments were generally well tolerated; the one adverse event reported was dizziness, which resulted in a fall from bed.

Mean plasma alprazolam concentrations are shown in Fig. 1, and alprazolam pharmacokinetics are summarized in Table 1. Alprazolam $AUC_{0\to5}$ and C_{max} after the first dose were increased 25% and 17%, respectively, by fluvoxamine. Plasma alprazolam concentrations on multiple dosing following the co-administration of fluvoxamine were increased approximately 2-fold relative to those after alprazolam alone; this was also reflected in the 2-fold increase in alprazolam $AUC_{0\to24}$ after fluvoxamine. Alprazolam clearance was significantly reduced by fluvoxamine; the t_{max} and V_z/f were not affected.

We obtained adequate fits of a one-compartment model to alprazolam concentrations from data from only 36 of 40 subjects (18 each in treatment groups b and c). The mean pharmacokinetic parameters obtained by curve-fitting are shown in Table 2. The results were similar to those obtained by non-compartmental methods, but, as expected, the estimated oral clearance obtained by curve-fitting for alprazolam in the presence of fluvoxamine was 18% smaller. Alprazolam λ_z was significantly reduced by fluvoxamine and the $t^1/_2$ was significantly increased.

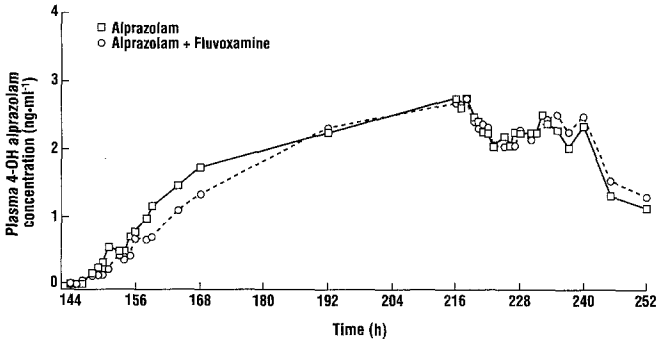

Fig. 2. Mean plasma concentrations of a-hydroxyalprazolam after 4.0 mg/day alprazolam alone or 100 mg/day fluvoxamine maleate plus 4.0 mg/day alprazolam in healthy male volunteers

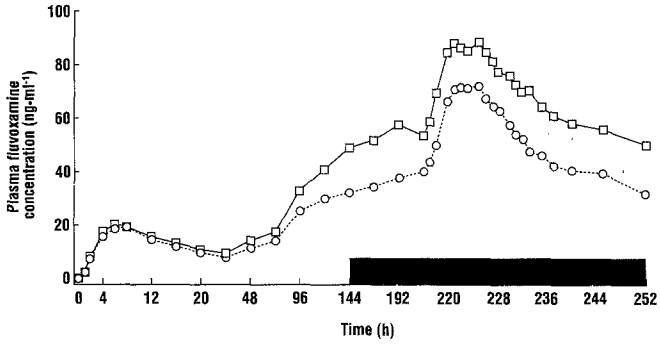

Fig. 3. Mean plasma concentrations of fluvoxamine after 100 mg/day fluvoxamine alone or 100 mg/day fluvoxamine maleate plus 4.0 mg/day alprazolam in healthy male volunteers. Note unequal spacing in the abscissa. The first alprazolam dose was given at 144 hours

The plasma concentrations of α-hydroxyalprazolam were generally below the limit of quantification. Plasma concentrations of 4-hydroxyalprazolam are shown in Fig. 2. Fluvoxamine administration had little effect on 4-hydroxyalprazolam plasma concentrations at steady state.

Mean plasma fluvoxamine plasma concentrations are shown in Fig. 3, and its pharmacokinetics are summarized in Table 3. There was little difference between the groups in fluvoxamine plasma concentrations on days 1–3. How-

Table 3. Mean fluvoxamine pharmacokinetics following fluvoxamine alone and fluvoxamine plus alprazolam

Parameter	Treatment	
	Fluvoxamine	Alprazolam + fluvoxamine
	Day 1	
$AUC_{0\to24}$ (ng·h·ml^{-1})	328 (84.6)	302 (111)
C_{max} (ng·ml^{-1})	21.5 (4.89)	20.7 (10.4)
t_{max} (h)	5.70 (1.49)	6.90 (1.65)
	Day 10	
$AUC_{0\to24}$ (ng·hr·ml^{-1})	1762* (737)	1341* (547)
C_{max} (ng·ml^{-1})	99.3* (35.0)	78.2* (25.3)
t_{max} (h)	7.95 (4.91)	6.90 (1.59)
λ_z (h^{-1})	0.031 (0.012)	0.026 (0.011)
$t_{1/2}$ (h)	27.2 (14.0)	31.4 (15.1)

* Significantly different by unpaired t-test at $P < 0.05$

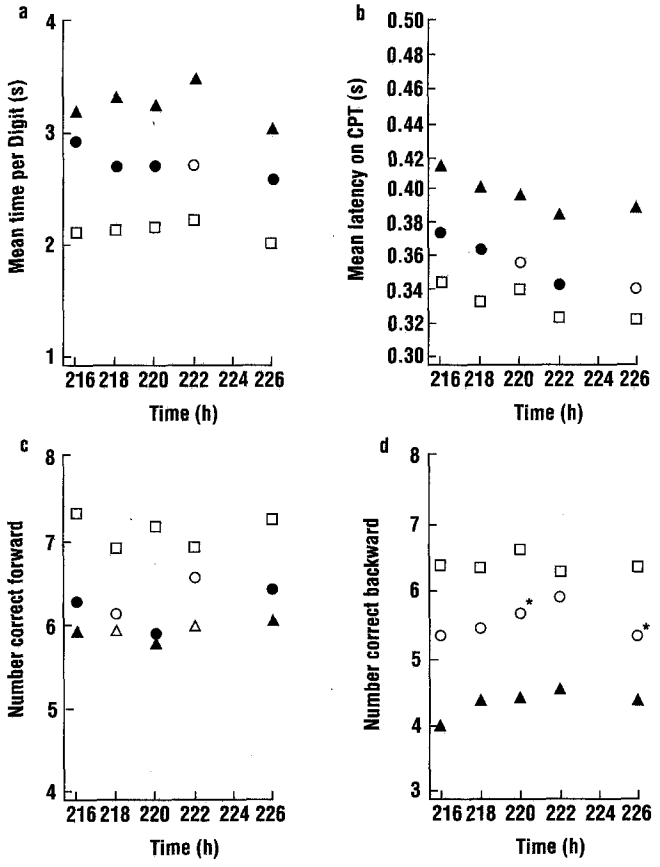

Fig. 4a–d. Mean scores for **a** symbol-digit substitution, **b** continuous performance, **c** digit-span forward, and **d** digit-span backward tests after 100 mg/day of fluvoxamine (□), 4.0 mg/day of alprazolam (○), or 100 mg/day of fluvoxamine plus 4.0 mg/day alprazolam (△) in healthy men. (Within times symbols with different shading are significantly different at $P < 0.05$. Asterisks in **d** denote that this value is not significantly different from the combination treatment)

ever, trough plasma concentrations of fluvoxamine were lower in the fluvoxamine + alprazolam group - from 96 to 252 h after the last dose. C_{max} and $AUC_{0\to24}$ on day 10 were significantly lower by about 25% for the fluvoxamine + alprazolam treatment versus fluvoxamine alone. Half-life and λ_z were not significantly different.

There were no significant treatment effects on psychomotor performance on day 1. On days 7 and 10, both SDS and CPT tests showed significant differences between treatments, especially on day 10. The results of the psychomotor performance tests on day 10 are shown in Fig. 4. Response latency times for SDS and CPT were generally longest for the fluvoxamine + alprazolam treatment. There were no significant differences in the digit-span number correct, except on day 10. The degree of sedation (data not shown) was not significantly different among treatments.

Discussion

Pharmacokinetics

Previous studies have shown that fluvoxamine inhibits hepatic metabolism [1, 2]. The results of this study show that fluvoxamine also reduces the hepatic metabolism of alprazolam. Although steady-state alprazolam concentrations were not achieved during the study, compartmental analysis of alprazolam concentrations confirm that alprazolam plasma concentrations were approximately doubled by fluvoxamine, reflecting changes in alprazolam clearance. The mechanism of this interaction has not been elucidated, but is most likely competitive inhibition of hepatic cytochrome P-450 (CYP) [2]. Protein binding is not a possible mechanism, since neither compound is highly protein bound [2, 13].

Plasma concentrations of 4-hydroxyalprazolam were not substantially affected by fluvoxamine, which could have been due to a lack of effect on the formation or elimination of 4-hydroxyalprazolam, which is primarily cleared by glucuronidation. This is consistent with the previously reported lack of effects of fluvoxamine on lorazepam glucuronidation [2]. However, plasma concentrations of the hydroxylated metabolites were too low to contribute significantly to the effects of alprazolam [7].

Fluvoxamine appears to be a potent inhibitor of the CYP1 A2 isozyme [14], in contrast to fluoxetine and paroxetine, which primarily inhibit CYP2 D6 [2]. Although the sample size was not sufficient for statistical comparison, smokers had lower fluvoxamine $AUC_{0\to24}$ (1535 (753)

$ng \cdot h \cdot ml^{-1}$) than non-smokers (1990 (669) $ng \cdot h \cdot ml^{-1}$). Since smoking induces CYP1 A2 [14], this observation is consistent with the metabolism of fluvoxamine by this isozyme. Alprazolam kinetics did not differ significantly between smokers and non-smokers, and the results of a previous study also suggest a minimal effect of smoking on alprazolam pharmacokinetics [15]. From this limited evidence, CYP1 A2 does not appear to be important in mediating alprazolam metabolism in man. Ketoconazole inhibits alprazolam metabolism *in vitro* (von Moltke et al., unpublished data) suggesting that CYP3 A4 primarily mediates alprazolam metabolism. The effects of fluvoxamine on CYP3 A4 have not been well studied, but the effects of fluvoxamine on imipramine demethylation, which may proceed via either CYP1 A2 or CYP3 A4 [14], suggest that fluvoxamine may inhibit this isozyme as well.

Alprazolam had little effect on the pharmacokinetics of fluvoxamine. From Fig. 4, it is obvious that the plasma fluvoxamine concentration versus time curves for the two groups were beginning to diverge by 144 hours after dosing. Up to this time, no alprazolam had been given to the alprazolam + fluvoxamine group. Moreover, the differences in fluvoxamine concentrations between groups were modest, of the order of 25 %. Therefore, differences between groups in fluvoxamine pharmacokinetics were probably due to inter-subject variability, rather than an effect of alprazolam on fluvoxamine metabolism.

Psychomotor performance tests

Acute administration of 50 mg fluvoxamine on day 1 had little effect on psychomotor performance. The data for SDS and CPT on days 7 and 10 are consistent with greater reductions in performance after the co-administration of alprazolam + fluvoxamine compared with both alprazolam and fluvoxamine alone. The interaction was apparent even on acute administration, as there were consistently significant differences between fluvoxamine + alprazolam and alprazolam alone on day 7, without consistent differences between alprazolam and fluvoxamine alone. These changes in performance are attributable to the increased plasma concentrations of alprazolam during co-administration of alprazolam and fluvoxamine.

Reductions in memory, assessed by the digit span test, were less robust than the reductions in psychomotor performance. However, the results were consistent with greater reductions after fluvoxamine + alprazolam than after alprazolam or fluvoxamine alone. There were no significant differences in sedation, although the trends in the sedation data were similar to those in the psychomotor and memory data. The lack of significant differences in sedation may have been due to the subjective nature of the rating scale used, the moderate degree of sedation observed, and variability in this measure.

Conclusions

Co-administration of alprazolam and fluvoxamine resulted in plasma concentrations of alprazolam approximately twice those observed with alprazolam alone. The increased plasma alprazolam concentrations resulted in greater reductions in psychomotor performance and memory. These results suggest that when alprazolam and fluvoxamine are co-administered, the dosage of alprazolam should be reduced.

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