

MINIMAL INTERACTION BETWEEN FLUOXETINE AND MULTIPLE-DOSE ZOLPIDEM IN HEALTHY WOMEN

STÉPHANE ALLARD, STEPHEN SAINATI, BARBARA ROTH-SCHECHTER, AND JOHN MACINTYRE

Lorex Pharmaceuticals (S.A., S.S., J.M.) and Boston Research and Science Consulting (B.R.-S.)

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ABSTRACT:

The objective was to evaluate possible pharmacokinetic and pharmacodynamic interactions for repeated nightly zolpidem dosing with fluoxetine. Twenty-nine healthy female volunteers (mean age, 25.6 years) received zolpidem (10 mg) and fluoxetine (20 mg) in the following open design: zolpidem on night 1 followed by 1 washout day, a daily morning dose of fluoxetine on days 3 through 27, and a morning dose of fluoxetine plus an evening dose of zolpidem on days 28 through 32. Plasma levels of zolpidem, fluoxetine, and norfluoxetine were determined at the transitions from one regimen to the next. Morning psychomotor tests were performed on days 1, 2, 28, 29, and 33. Steady-state plasma concentrations of fluoxetine/norfluoxetine were reached by day 24 of fluoxetine dosing. No significant differences in any pharmacokinetic parameters for fluoxetine and norfluoxetine were observed between day 27 and day

32. There were no significant differences in AUC, maximal plasma concentration, or time to maximal concentration parameters for zolpidem plasma concentrations among nights 1, 28, and 32. There was a statistically significantly increased $t_{1/2}$ for zolpidem on night 32, compared with night 28 (3.64 and 3.29 hr, respectively). There were no significant differences in the next-morning Digit Symbol Substitution Test performance at any time in the study. Both zolpidem and fluoxetine were well tolerated alone or during coadministration. These findings indicate the absence of clinically significant pharmacokinetic or pharmacodynamic interactions between fluoxetine and zolpidem (five consecutive doses) when the drugs are coadministered to healthy women. Therefore, based on these observations, short-term cotherapy with fluoxetine (20 mg) and zolpidem (10 mg) appears safe.

SSRIs¹ such as fluoxetine constitute a new generation of antidepressant drugs (Goodwin, 1996). The popularity of the SSRIs is largely attributable to their convenience, their generally more favorable side-effect profile, and their safety in overdose (Thase and Kupfer, 1996). However, with other serotonin-related side effects, insomnia has been reported to be a significant treatment effect for SSRIs in general (Ware and Morowitz, 1991) and for fluoxetine in particular (Thase *et al.*, 1997). Independent of its antidepressant effect, fluoxetine significantly modifies sleep parameters and sleep architecture (Gillin *et al.*, 1997). To provide maximal benefits to depressed patients with insomnia, SSRIs are often coadministered with a sedative/hypnotic drug (Neylan, 1995; Cook and Conner, 1995; Mendelson, 1990).

Fluoxetine is one of the most frequently prescribed SSRI antidepressant drugs (Boyer and Feighner, 1991). It has a half-life of 4–6 days after chronic administration, and steady-state plasma concentrations are reached after approximately 3 weeks of daily treatment. The major metabolite of fluoxetine is norfluoxetine, which is also an active SSRI with a half-life of 4–16 days (DeVane, 1992). The potential for

drug interactions with fluoxetine exists because of its effect on the hepatic microsomal system. Fluoxetine is a substrate and inhibitor of the CYP2D6 and CYP2C9/10 isoenzymes, and it moderately inhibits CYP2C19 as well (Preskorn, 1997). Norfluoxetine is a potent inhibitor of the CYP3A4 system (Riesenman, 1995).

Zolpidem is an imidazopyridine hypnotic agent, with a half-life of approximately 2.5 hr, that is metabolized in the liver to inactive alcohol derivatives (Thénot *et al.*, 1988). This reaction is principally mediated by CYP3A4 and appears to be the rate-limiting reaction (Pichard, 1995). CYP1A2 and CYP2D6 contribute to a minor extent to the metabolism of zolpidem (Pichard, 1995). Based on its kinetic parameters, with no active metabolites and a good efficacy/safety profile (Freeman *et al.*, 1996; Uden and Roth-Schechter, 1996; Piergies *et al.*, 1996), zolpidem could be useful as a co-medication administered with fluoxetine to relieve insomnia and enable patients to sleep.

In clinical situations, when a SSRI is coadministered with a hypnotic agent the latter is likely to be used repeatedly for several consecutive nights. We report here the results of a standardized prospective study, with healthy female volunteers, of administration of repeated doses of zolpidem (10 mg) in the presence of steady-state concentrations of fluoxetine. This study population was of particular interest because depression, as well as insomnia, appears to be more prevalent in women than in men (Mendelson, 1990; American College of Obstetrics and Gynecology, 1993).

Subjects and Methods

Subjects. After Institutional Review Board approval and informed patient consent were obtained, 99 female subjects were enrolled in the

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¹ Abbreviations used are: SSRI, selective serotonin reuptake inhibitor; DSST, Digit Symbol Substitution Test; C_{24} , plasma concentration at 24 hr after fluoxetine dosing; TEAE, treatment-emergent adverse event; C_{max} , maximal plasma concentration; T_{max} , time to maximal plasma concentration; ANOVA, analysis of variance; CYP, cytochrome P450.

Send reprint requests to: Stéphane Allard, M.D., Lorex Pharmaceuticals, P.O. Box 5110, Chicago, IL 60680-5110.

TABLE 1
Study design and treatment sequence

Treatment Day/Night	Morning Treatment	Evening Treatment	Blood Sampling	Environment	Pharmacodynamic Testing
1		Zolpidem	Zolpidem	Admission/CPU	DSST, Trails A & B
2			Zolpidem	CPU	DSST, Trails A & B
3	Fluoxetine			CPU/discharge	
4–24	Fluoxetine			Outpatient	
25 & 26	Fluoxetine		Fluoxetine/NF	Outpatient	
27	Fluoxetine		Fluoxetine/NF	Admission/CPU	
28	Fluoxetine	Zolpidem	Fluoxetine/NF, zolpidem	CPU	DSST, Trails A & B
29	Fluoxetine	Zolpidem	Zolpidem	CPU	DSST, Trails A & B
30 & 31	Fluoxetine	Zolpidem		CPU	
32	Fluoxetine	Zolpidem	Fluoxetine/NF, zolpidem	CPU	
33			Fluoxetine/NF, zolpidem	CPU	DSST, Trails A & B
34			Fluoxetine/NF	CPU/discharge	
37			Fluoxetine/NF	Outpatient	
40			Fluoxetine/NF	Outpatient	

NF, norfluoxetine; CPU, Clinical Pharmacology Unit.

study. Subjects were required to exhibit good health, as determined by medical history, physical examination, and laboratory analysis. Any significant medical or psychiatric disorder, pregnancy (or the risk of becoming pregnant), or lactation excluded subjects from participation. A history of sensitivity to central nervous system depressants, a recent history of alcohol or drug abuse, smoking within the previous 6 months, donation of blood within 60 days of study entry, use of any investigational drug within 30 days of study entry, or use of oral over-the-counter or prescription medications (except for contraceptives and topical ointments) also excluded subjects. Of the enrolled subjects, 49 discontinued participation before the start of active treatment, primarily because of screening failures (34 subjects) or for administrative reasons (14 subjects). Of the 50 subjects who received active treatment, 24 completed the study; 21 discontinued participation for administrative reasons, 3 because of adverse events/abnormal laboratory test results, and 2 for noncompliance with study procedures. Of the 21 subjects who discontinued participation for administrative reasons, 19 did not have a specified blood sample taken after the first zolpidem dosing. Because this measurement was used to calculate both T_{\max} and C_{\max} values for zolpidem, its absence would have compromised the evaluation of the pharmacokinetic data. The error was reported to the sponsor within 24 hr, and the decision was made by the sponsor to discontinue study drug dosing to this cohort of subjects. The three subjects who discontinued therapy because of an adverse event were as follows. One 22-year-old subject discontinued participation 25 days after the start of therapy with fluoxetine alone because of a spontaneous abortion. Another 22-year-old subject discontinued participation because of a rash that first appeared 3 days after the start of zolpidem/fluoxetine combination therapy. Lastly, a 23-year-old subject discontinued participation because of erythema multiforme on day 2 of zolpidem/fluoxetine combination therapy. A total of 29 subjects (mean age, 25.6 years; range, 20–45 years; mean weight, 62.2 kg; range, 45–88 kg) yielded data for at least two time points assessing pharmacokinetic and/or pharmacodynamic outcome measures after the start of active treatment. Data from these 29 subjects were used for analyses. All 50 subjects who received active treatment were included in the assessment of safety.

Study Design. This was an open-label, fixed-treatment-sequence study in which pharmacokinetic parameters for zolpidem, fluoxetine, and norfluoxetine and pharmacodynamic outcome measures were assessed after single nighttime doses of zolpidem (10 mg) and after five consecutive nightly oral doses of zolpidem (10 mg) administered either alone or in the presence of steady-state plasma concentrations

of fluoxetine. A summary of the treatment sequence is presented in table 1.

Sample Collection. Serial 5-ml venous blood samples for the determination of zolpidem plasma levels were collected before the evening dose of zolpidem and over the next 24 hr (at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hr after zolpidem dosing) on nights 1, 28, and 32. A single 7-ml venous blood sample for the determination of fluoxetine and norfluoxetine plasma levels was collected before the morning dose of fluoxetine on days 25, 26, and 27. Serial 7-ml samples were also obtained over a 24-hr period (at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 18, and 24 hr after fluoxetine dosing) on day 27 and over a 192-hr period (at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 36, 48, 120, and 192 hr after dosing) starting on day 32.

Pharmacokinetic Assays and Analysis. Plasma samples were assayed for zolpidem, fluoxetine, and norfluoxetine levels, which were determined by HPLC according to previously validated methods (Wong *et al.*, 1990; Thénot *et al.*, 1988) and were used to calculate the following pharmacokinetic parameters for zolpidem: AUC_{0-24} , C_{\max} , T_{\max} , and $t_{1/2}$. Based on plasma fluoxetine/norfluoxetine levels, AUC_{0-24} , C_{\max} , T_{\max} , and $t_{1/2}$ (fluoxetine only) values were calculated.

All AUC values were estimated using the trapezoidal rule. The elimination rate (also used in the calculation of $t_{1/2}$) was calculated from the logarithmic-linear portion of the curve, using linear regression applied to the logarithmic concentrations.

Pharmacodynamic Evaluation. The DSST scores and the times required to complete trail-making tests A and B were compared at 9 hr after zolpidem treatment on the following mornings: day 1 (no drug, familiarization), day 2 (zolpidem alone), day 28 (fluoxetine alone), and days 29 and 33 (combination of zolpidem, in a single dose or five consecutive doses, respectively, and fluoxetine). The DSST sequence was different for different days, but the trail-making tests were the same for each testing period. The analyzed measure for the DSST was total number of correct substitutions during a 3-min period and that for the trail-making test was the time necessary to complete the test (in seconds).

Statistical Analysis. Equivalence of a given drug across two or more time points was tested by comparing variables using ANOVA. The ANOVA model contained terms for subject and for day. If significant ($p < 0.05$) overall differences between days were observed and more than 2 days were compared, then pairwise differences were compared using the Fisher least-significant difference test applied to the least-square means. In addition, the ratios of each of the pharmacokinetic parameters were calculated and 95% confidence intervals

TABLE 2

Trough plasma concentrations of fluoxetine/norfluoxetine in female subjects (N = 29) who received 20 mg of fluoxetine every 24 hr

	C_{24}				Overall <i>p</i>
	Day 24	Day 25	Day 26	Day 27	
	ng/ml				
Fluoxetine	98.31 ± 8.84 ^a	99.38 ± 8.48 ^{a,b}	104.69 ± 8.62 ^c	103.42 ± 9.29 ^{b,c}	0.007
Norfluoxetine	135.06 ± 6.98 ^a	141.11 ± 6.45 ^{b,c}	147.84 ± 6.78 ^d	144.58 ± 6.86 ^{c,d}	<0.001

Data are mean values ± SE.

^{a-d} Means marked with the same letter are not significantly different.

were derived. Fieller's theorem was used to calculate 95% confidence intervals. A mean ratio of 1.0, with the 95% confidence interval being included entirely within the range of 0.8–1.25, was the criterion used for bioequivalence.

The attainment of steady-state plasma concentrations of fluoxetine/norfluoxetine on day 27 was assessed by using a paired *t* test to compare the C_{24} values on days 24 and 27. Additionally, comparisons of all four trough observations on days 24–27 were compared by ANOVA, with terms for subject and day.

Safety. Safety was assessed by collection of adverse events from spontaneous reports and physical examination, review of vital signs, and clinical laboratory test results. Safety analyses included all subjects who received at least one dose of study medication.

Results

Trough fluoxetine and norfluoxetine plasma concentrations on days 24–27 are summarized in table 2. In both cases, comparisons of C_{24} across days 24 through 27 showed significant overall differences, with day 24 being significantly different from day 27. However, plasma levels of either fluoxetine or norfluoxetine on day 27 did not differ significantly from those on either day 26 or day 25. It is apparent that, although steady-state conditions had not been reached by day 24, they had been reached by day 27 for both fluoxetine and norfluoxetine.

The time courses of zolpidem plasma concentrations on day 1 (zolpidem alone), on day 28 (one dose of zolpidem in the presence of fluoxetine), and on day 32 (fifth consecutive daily dose of zolpidem in the presence of fluoxetine) are shown in fig. 1. At no time point was there any statistically significant difference among the sampling days, *i.e.* when a single dose of zolpidem was given alone or in the presence of fluoxetine or after five consecutive doses of zolpidem in the presence of fluoxetine. Similarly, the time course profiles for fluoxetine/norfluoxetine plasma concentrations at steady state in the absence of zolpidem (day 27) were indistinguishable from those observed for fluoxetine/norfluoxetine in combination with zolpidem (day 32) (fig. 2). The specific pharmacokinetic parameters for zolpidem, fluoxetine, and norfluoxetine, administered alone or coadministered, are summarized in table 3. After one or five consecutive doses of zolpidem (10 mg), there were no significant differences in AUC, C_{max} , or T_{max} values for zolpidem, irrespective of whether it was administered alone or in the presence of steady-state plasma concentrations of fluoxetine/norfluoxetine. There were also no significant changes in any of the pharmacokinetic parameters for fluoxetine/norfluoxetine when they were determined at steady state in the presence of one dose or five consecutive doses of zolpidem. The only statistically significant difference detected was a higher value (+21 min) for the half-life of zolpidem on day 32 (fifth consecutive nightly dose of zolpidem in the presence of fluoxetine/norfluoxetine), compared with day 28 (one dose of zolpidem in the presence of fluoxetine/norfluoxetine) or day 1 (zolpidem alone).

Mean ratios for the concentration parameters AUC and C_{max} for zolpidem and AUC, C_{max} , and C_{24} for fluoxetine/norfluoxetine, with

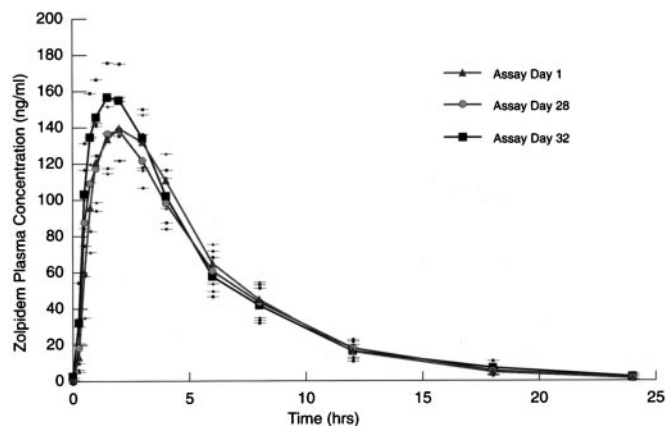


FIG. 1. Plasma concentration-time profiles for zolpidem in healthy female volunteers.

Subjects received an evening dose of zolpidem (10 mg) (day 1), followed by 1 washout day. Subjects then received a morning dose of fluoxetine (20 mg) for 30 consecutive days (days 3 through 32). On days 28 through 32, subjects also received an evening dose of zolpidem. Plasma concentrations were measured on day 1 (zolpidem alone), on day 28 (single dose of zolpidem plus fluoxetine), and on day 32 (fifth consecutive dose of zolpidem plus fluoxetine). Data represent means ± 2 SE.

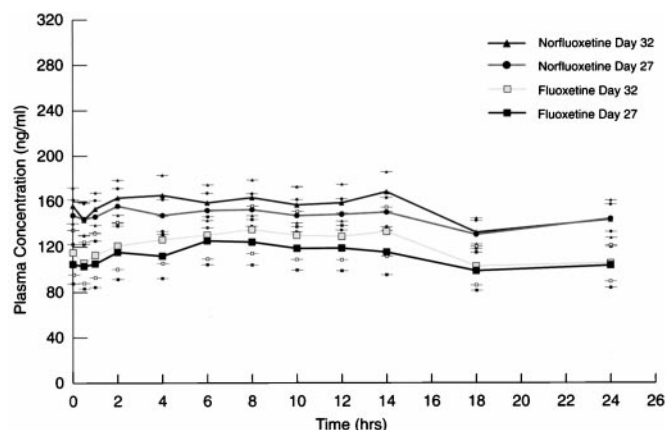


FIG. 2. Plasma concentration-time profiles for fluoxetine and norfluoxetine in healthy female volunteers.

For treatment sequences, refer to the legend to fig. 1. Plasma concentrations were measured on day 27 (fluoxetine only) and on day 32 (fluoxetine in the presence of the fifth consecutive daily dose of zolpidem). Data represent means ± 2 SE.

the respective 95% confidence intervals, are presented in table 4. The mean zolpidem concentration ratios (using day 1 as the reference) and 95% confidence intervals were estimated to assess the bioavailability of zolpidem in the presence and absence of fluoxetine. Similarly, ratios of both fluoxetine and norfluoxetine concentration measures when fluoxetine was given after five consecutive nightly zolpidem doses (day 32) to the same measures when fluoxetine was given alone

TABLE 3

Pharmacokinetic parameters for zolpidem and fluoxetine/norfluoxetine in female subjects (N = 29) during coadministration of zolpidem (10 mg) and fluoxetine (20 mg)

Treatment	AUC ₀₋₁₂ ng·hr/ml	AUC ₀₋₂₄ ng·hr/ml	C _{max} ng/ml	T _{max} hr	T _{1/2} hr
ZPD					
Day 1 (ZPD only)	853.5 ± 55.48	934.9 ± 66.04	163.52 ± 7.74	1.81 ± 0.19	3.11 ± 0.15
Day 28 (FLU + ZPD)	824.1 ± 55.19	917.04 ± 69.03	167.94 ± 8.92	1.67 ± 0.24	3.29 ± 0.15
Day 32 (FLU + 5 ZPD)	878.0 ± 64.04	978.77 ± 83.63	175.91 ± 9.98	1.54 ± 0.19	3.64 ± 0.24 ^a
FLU					
Day 27 (FLU only)	NA ^b	2674.53 ± 226.44	133.48 ± 11.09	8.28 ± 0.82	NA
Day 32 (FLU + 5 ZPD)	NA	2879.63 ± 229.71	142.23 ± 10.85	9.04 ± 0.92	88.12 ± 7.22 ^c
Norfluoxetine					
Day 27 (FLU only)	NA	3487.31 ± 158.90	165.57 ± 7.59	6.40 ± 1.02	
Day 32 (FLU + 5 ZPD)	NA	3674.90 ± 178.62	177.44 ± 8.49	11.04 ± 1.93	

ZPD, Zolpidem; FLU, Fluoxetine.

^a Significantly different from days 1 and 28 ($p < 0.05$).

^b NA, not applicable.

^c N = 24 at day 32.

TABLE 4

Mean ratios of concentration measures for zolpidem, fluoxetine, and norfluoxetine administered alone or in combination

Zolpidem Parameter	Day 28	Day 32
AUC ₀₋₂₄ (ng·hr/ml)		
Ratio	0.977	1.036
95% CI ^a	0.854–1.113	0.900–1.189
C _{max} (ng/ml)		
Ratio	1.027	1.043
95% CI	0.937–1.123	0.954–1.136
Fluoxetine/norfluoxetine Parameter	Fluoxetine	Norfluoxetine
AUC ₀₋₂₄ (ng·hr/ml)		
Ratio	1.028	1.023
95% CI	0.974–1.091	0.983–1.065
C _{max} (ng/ml)		
Ratio	1.018	1.038
95% CI	0.956–1.091	0.985–1.093
C ₂₄ (ng/ml)		
Ratio	0.976	0.967
95% CI	0.903–1.067	0.904–1.031

^a CI, confidence interval.

under steady-state conditions (day 27) were determined. All ratios were close to unity, and all confidence intervals were within the range of 0.8–1.25, indicating that the bioavailabilities of zolpidem and fluoxetine/norfluoxetine were equivalent when the drugs were administered alone or were coadministered.

No significant effects of zolpidem, in the absence or presence of fluoxetine, on the abilities of the subjects to perform the DSST at 9 hr after drug administration could be detected (table 5). Different DSST forms were used on each of the days. The numbers of correct substitutions were 129.55 ± 2.77 on day 2 (zolpidem only), 131.55 ± 3.13 on day 28 (fluoxetine only), 128.29 ± 3.51 on day 29 (fluoxetine plus one dose of zolpidem), and 131.00 ± 3.15 on day 33 (fluoxetine plus five doses of zolpidem). The performance on the trail-making tests improved progressively from day 2 to day 33. The same trail A and B forms, however, were used throughout the study.

TEAE incidence rates of $\geq 5\%$ are presented in table 6. These incidence rates cannot be easily compared between treatment with zolpidem or fluoxetine alone and coadministration, because the treatment periods were different in duration and environment. With the exception of those adverse events that led to study discontinuation (see *Materials and Methods*), all adverse events were of mild or moderate severity and resolved without sequelae. It is noteworthy that fluoxetine treatment alone showed a high incidence of anorexia (14%)

and insomnia (6%), neither of which occurred during the fluoxetine/zolpidem coadministration period. On the other hand, higher incidences of headache (17%), dizziness (7%), and diplopia (7%) were noted during the fluoxetine/zolpidem coadministration period.

Discussion

The results of this study indicated that steady-state fluoxetine/norfluoxetine plasma levels were achieved by day 24 of daily morning administration of fluoxetine (20 mg) (table 2) to healthy female volunteers. Therefore, comparison of pharmacokinetic parameters before and after this treatment period with coadministration of zolpidem, at a single or repeated 10-mg dose, was meaningful.

Zolpidem is biotransformed to a series of oxidized inactive metabolites. This transformation is principally mediated by CYP3A4 and constitutes the rate-limiting step. A number of drugs, including erythromycin, midazolam, imipramine, terfenadine, and others, are substrates for CYP3A4 and thus are metabolized *via* that route. No pharmacokinetic interactions between single doses of zolpidem and chlorpromazine, haloperidol, or imipramine have been detected (Harvent *et al.*, 1988). Furthermore, no clinically significant pharmacokinetic or pharmacodynamic interactions were reported between a single dose of zolpidem (10 mg) and fluoxetine in healthy male volunteers (Piergies *et al.*, 1996).

The SSRIs have considerable potential for drug interactions (Lane, 1996), including those with sedative/hypnotic drugs. The clearance of several benzodiazepines (alprazolam and diazepam) is impaired by fluoxetine (Fleishaker and Hulst, 1991; Lemberger *et al.*, 1988). One study of *in vivo* interactions between fluoxetine and triazolam reported no significant pharmacokinetic interactions; however, steady-state plasma concentrations of fluoxetine had not been attained (Wright *et al.*, 1992). Pharmacodynamic interactions between estazolam (another benzodiazepine hypnotic agent) and fluoxetine, resulting in increased impairment of DSST performance and of hand-eye coordination, have been reported, but without measurable pharmacokinetic interactions between the two drugs (Cavanaugh *et al.*, 1994). On the other hand, pharmacokinetic interactions were observed with diazepam, without significant pharmacodynamic interactive complications (Lemberger *et al.*, 1988).

The results of the present study are in agreement with the concept that coadministration of therapeutic doses of CYP3A4 substrates does not necessarily produce significant pharmacokinetic interactions, probably because of the large capacity of this metabolizing system. The present observations could be considered an extension of the previous study of single-dose zolpidem coadministration to male

TABLE 5

Pharmacodynamic parameters in female subjects (N = 29) during coadministration of zolpidem (10 mg) and fluoxetine (20 mg)

Test	Day 2 (ZPD only) (N = 29)	Day 28 (FLU only) (N = 29)	Day 29 (FLU + ZPD) (N = 28)	Day 33 (FLU + 5 ZPD) (N = 25)	Overall p value
DSST (no. of correct substitutions)	129.55 ± 2.77	131.55 ± 3.13	128.29 ± 3.51	131.00 ± 3.15	0.407
Trail A (sec)	18.30 ± 0.87 ^{a,b}	18.88 ± 1.23 ^a	16.88 ± 0.86 ^b	15.29 ± 0.88 ^c	<0.001
Trail B (sec)	36.92 ± 2.11 ^{a,b}	38.24 ± 2.00 ^a	33.00 ± 1.92 ^b	33.06 ± 2.47 ^b	0.005

ZPD, zolpidem; FLU, fluoxetine.

^{a-c} Within each test, means marked with the same letter are not significantly different.

TABLE 6

TEAE that occurred in ≥5% of subjects in any treatment group

TEAEs	No. of Events		
	Zolpidem (N = 50)	Fluoxetine (N = 50)	Zolpidem + Fluoxetine (N = 29)
Anorexia	0 (0.0%)	7 (14.0%)	0 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	2 (6.9%)
Diplopia	1 (2.0%)	0 (0.0%)	2 (6.9%)
Erythema multiforme	0 (0.0%)	0 (0.0%)	2 (6.9%)
Headache	1 (2.0%)	5 (10.0%)	5 (17.2%)
Insomnia	0 (0.0%)	3 (6.0%)	0 (0.0%)
Nausea	1 (2.0%)	7 (14.0%)	1 (3.4%)
Pharyngitis	0 (0.0%)	0 (0.0%)	2 (6.9)
Teeth grinding	0 (0.0%)	3 (6.0%)	0 (0.0%)
Overall	7 (14.0%)	21 (42.0%)	15 (51.7%)

subjects (Piergies *et al.*, 1996) to multiple-night administration of zolpidem to healthy female subjects.

The statistically significant increase in the half-life of zolpidem (by 21 min, from 3.29 to 3.64 hr) between the first and fifth doses of zolpidem in the presence of fluoxetine (table 3) could be the result of a slowing of zolpidem metabolism. It is likely to be clinically inconsequential, however, given that zolpidem is administered as a single nightly dose and that the dosing interval is >5 half-lives using either half-life estimate. The risk of drug accumulation, and of any side effects associated with drug accumulation, appears minimal at these doses. The absence of any changes in AUC, C_{max} , and T_{max} values for zolpidem and/or fluoxetine/norfluoxetine, together with the absence of any changes in the bioavailability of either drug (table 4), confirms such an interpretation. The present results can be put in perspective by comparison with the approximately 25-fold increase in the AUC of triazolam (a short-acting benzodiazepine hypnotic agent) resulting from CYP3A4 inhibition by ketoconazole (Varhe *et al.*, 1994).

Although comparisons among study populations in different studies are inherently difficult, it is tempting, for two reasons, to compare the results of the present trial with female subjects with the results of our similar study with male volunteers (Piergies *et al.*, 1996). Firstly, there is the question of gender-related differences in the pharmacokinetic parameters of zolpidem and fluoxetine administered alone. AUC_{0-12} , C_{max} , and $t_{1/2}$ values for zolpidem were greater for the female subjects in the present study than for the male subjects, and the T_{max} for zolpidem was reached earlier with the female subjects. This gender discrepancy is in agreement with previously published observations (Bianchetti *et al.*, 1988). When the differences between the two populations in weight, height, and body surface area were taken into account, approximately one half of these differences between male and female subjects were accounted for. There is no obvious explanation for the remaining differences, but similar results have been reported (Bianchetti *et al.*, 1988). It is noteworthy that, although the adjusted mean values for female subjects were higher than those for male subjects, they were within the ranges of published values for male subjects (Medical Economics Company, PDR, 1997). The pharmacokinetic data for fluoxetine cannot be compared, because the

treatment durations were different in the two studies (16 vs. 24 days). Secondly, there is the question of gender-related differences in the zolpidem/fluoxetine interaction. Only the data for the single dose of zolpidem in the presence of steady-state plasma concentrations of fluoxetine can be compared, and it should be appreciated that plasma sampling for the zolpidem determinations occurred more often in the early portion of the present study than in the male-subject trial. Overall, and with all of the limitations of this comparison, it appears that there are no significant gender-related differences in the metabolism of zolpidem or the zolpidem/fluoxetine interaction.

Decrease in DSST performance is an accepted measure of next-day impairment by hypnotic agents after nighttime administration (Roehrs *et al.*, 1986; Roth *et al.*, 1985, 1994). In the present study, there were no differences in next-day performance on the DSST, whether zolpidem was administered alone or in the presence of fluoxetine as a single dose or multiple doses. The statistically significant enhancement of performance on the trail-making test is likely the result of progressive learning by the subjects, because the same trail-making design was used repeatedly. Based on the DSST results, there were no pharmacodynamic interactions between consecutively (nighttime) administered zolpidem and fluoxetine at steady-state plasma concentrations. The significance of this interpretation, however, must be kept in perspective, because this study was of an open, fixed-treatment design and the comparisons are between study segments rather than between parallel groups.

No serious or unexpected adverse events occurred during the study. The most commonly reported TEAE was headache during the period of zolpidem plus fluoxetine coadministration. TEAE incidences are difficult to compare, because the treatment periods and environments were not comparable. A recent case report suggested a possible interaction between zolpidem and SSRIs, resulting in hallucinations (Elko *et al.*, 1996). There were no hallucinations reported in the present study with any treatment regimen. There was, however, a 7% incidence of diplopia when zolpidem and fluoxetine were administered together, compared with a 2% incidence when zolpidem was administered alone and a 0% incidence when fluoxetine was administered alone. Overall, the drug safety assessment did not reveal problems that had not been previously identified for either agent alone.

In view of the need for a short-acting hypnotic agent for potential coadministration with the SSRIs, the apparent absence of any clinically significant interaction between therapeutic doses of zolpidem and fluoxetine is of clinical importance. Therefore, based on these observations, short-term coadministration of fluoxetine (20 mg) and zolpidem (10 mg) appears safe.

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References

- American College of Obstetrics and Gynecology (1993) ACOG technical bulletin 182: depression in women. *Int J Gynecol Obstet* 43:203-211.
- Bianchetti G, Dubruc C, Thiercelin JF, et al. (1988) Clinical pharmacokinetics of zolpidem in

- various physiological and pathological conditions, in *Imidazopyridines in Sleep Disorders* (Sauvanet JP, Langer SZ and Morselli PL eds) pp 155–164, Raven Press, New York.
- Boyer WF and Feighner JP (1991) The efficacy of selective serotonin reuptake inhibitors in depression, in *Selective Serotonin Uptake Inhibitors* (Feighner JP and Boyer WF eds) pp 89–108, Wiley, Chichester, UK.
- Cavanaugh J, Schneck D and Eason C (1994) Lack of effect of fluoxetine on the pharmacokinetics and pharmacodynamics of estazolam. *Clin Pharmacol Ther* **55**:141.
- Cook MD and Conner J (1995) Retrospective review of hypnotic use in combination with fluoxetine and sertraline. *Clin Drug Invest* **9**:212–216.
- DeVane CL (1992) Pharmacokinetics of selective serotonin reuptake inhibitors. *J Clin Psychiatry* **53**(Suppl 2):13–20.
- Elko CJ, Burgess JL and Robertson WO (1996) Zolpidem (Ambien®) and serotonin reuptake inhibition: possible interaction. *North American Congress of Clinical Toxicology Abstr* 566.
- Fleishaker JC and Hulst LK (1991) Pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology (Berlin)* **104**:323–327.
- Freeman H, Puech AJ and Roth T eds (1996) *Zolpidem: An Update of Its Pharmacological Properties and Therapeutic Place in the Management of Insomnia*. Elsevier, Paris.
- Gillin JC, Rapaport M, Erman MK, Winokur A and Albala BJ (1997) A comparison of nefazodone and fluoxetine on mood and on objective, subjective and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. *J Clin Psychiatry* **58**:185–192.
- Goodwin GM (1996) How do antidepressants affect serotonin receptors? The role of serotonin receptors in the therapeutic and side effect profile of the SSRIs. *J Clin Psychiatry* **57**(Suppl 4):9–13.
- Harvent C, Hulhoven R, Desager J, Coupez JM, Guillet PH, Fuseau E, Lambert D and Warrington SJ (1988) Drug interactions investigated with zolpidem, in *Imidazopyridines in Sleep Disorders: A Novel Experimental and Therapeutic Approach* (Sauvanet JP, Langer SZ and Morselli PL eds) pp 165–173, Raven Press, New York.
- Lane RM (1996) Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. *Int J Clin Psychopharmacol* **11**(Suppl 5):31–61.
- Lemberger L, Rowe H, Bosonworth JC, Tenbarga JB and Bergstrom RF (1988) The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. *Clin Pharmacol Ther* **43**:412–419.
- Mendelson WB (1990) Hypnotics in the treatment of chronic insomnia, in *Handbook of Sleep Disorders* (Thorpy MG ed) pp 737–753, Marcel Dekker, New York.
- Neylan CN (1995) Treatment of sleep disturbances in depressed patients. *J Clin Psychiatry* **56**(Suppl 2):56–61.
- Medical Economics Company (1997) Ambien labeling, in *Physicians' Desk Reference*, p 2F10, Oradell, NJ.
- Pichard L, Gillet G, Bonfils C, Domergue J, Thénot J-P and Maurel P (1995) Oxidative metabolism of zolpidem by human liver cytochrome P450s. *Drug Metab Dispos* **23**:1253–1262.
- Piergies AA, Roth-Schechter B, Shinleber P, McGarry L and Allard S (1996) Pharmacokinetic and pharmacodynamic interaction of zolpidem and fluoxetine. *Int J Clin Pharmacol Ther* **34**:178–183.
- Preskorn SH (1997) Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* **32**(Suppl 1):1–21.
- Riesenman C (1995) Antidepressant drug interactions and the cytochrome P450 system: a critical appraisal. *Pharmacotherapy* **15**:84S–99S.
- Roehrs T, Kribbs N, Zorick F and Roth T (1986) Hypnotic residual effects of benzodiazepines with repeated administration. *Sleep* **9**:309–316.
- Roth T, Hauri P, Zorick F, Sateia M, Roehrs T and Kipp J (1985) The effect of midazolam and temazepam on sleep and performance when administered in the middle of the night. *J Clin Psychopharmacol* **5**:66–69.
- Roth T, Roehrs TA, Vogel GW and Dement WC (1994) Evaluation of hypnotic medications, in *Clinical Evaluations of Psychotropic Drugs: Principles and Guidelines* (Prien RF and Robinson DS eds) p 579, Raven Press, New York.
- Thase ME, Blomgren SL, Birkett MA, Apter JT and Tepner RG (1997) Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. *J Clin Psychiatry* **58**:16–21.
- Thase ME and Kupfer DJ (1996) Recent developments in the pharmacotherapy of mood disorders. *J Consult Clin Psychol* **64**:646–659.
- Thénot JP, Hermann P, Durand A, et al. (1988) Pharmacokinetics and metabolism of zolpidem in various animal species and in humans, in *Imidazopyridines in Sleep Disorders* (Sauvanet JP, Langer SZ and Morselli PL eds) pp 139–153, Raven Press, New York.
- Uden M and Roth-Schechter B (1996) Next day effects after nighttime treatment with zolpidem: a review. *Eur J Psychiatry* **11**(Suppl 1):21S–30S.
- Varhe A, Olkkola KT and Neuvonen PJ (1994) Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* **56**:601–607.
- Ware JC and Morowitz J (1991) Diagnosis and treatment of insomnia and depression. *J Clin Psychiatry* **52**(Suppl 6):55–61.
- Wong SH, Dellafera SS, Fernandes R and Kranzler H (1990) Determination of fluoxetine and norfluoxetine by high-performance liquid chromatography. *J Chromatogr* **499**:601–608.
- Wright CE, Lasher-Sisson TA, Steenwyk RC and Swanson CN (1992) A pharmacokinetic evaluation of the combined administration of triazolam and fluoxetine. *Pharmacotherapy* **12**:103–106.