Pharmacokinetic and Pharmacodynamic Comparison of Immediate-Release and Sustained-Release Adinazolam Mesylate Tablets After Single- and Multiple-Dose Administration

Joseph C. Fleishaker[1,2] and C. Eugene Wright[1]

Received April 19, 1991; accepted October 22, 1991

The effect of adinazolam release rate on psychomotor performance and sedation was assessed by administering 40 mg adinazolam mesylate immediate-release (CT) tablets, 60 mg sustained-release (SR) tablets, and placebo in a double-blind crossover study in 15 healthy male subjects. A separate panel of 16 subjects received the above single doses and multiple-dose regimens of 40 mg CT tablets every 8 hr and 60 mg SR tablets every 12 hr according to a crossover design. Psychomotor performance was assessed by digit symbol substitution test, card sorting tasks, and sedation ratings. Following single-dose administration, dose-corrected adinazolam and *N*-desmethyladinazolam (NDMAD) AUC values were equivalent for SR and CT tablets. Peak adinazolam and NDMAD levels were lower and occurred later for the SR tablets. Decrements in card sorting were 50 and 3% at 1 hr and 17 and 20% at 6 hr for the CT and SR tablets, respectively. Maximal sedation scores were lower for the SR tablets compared to the CT. Dose-corrected AUC was comparable between single and multiple doses for both adinazolam and NDMAD; no differences were observed in 24-hr AUC at steady-state between CT and SR tablets. Fluctuation ratios were reduced for both adinazolam and NDMAD following SR tablets. Psychomotor and sedative effects were attenuated upon multiple dosing. Thus, the reduction in peak plasma NDMAD following SR tablet administration results in a lesser sedation and psychomotor impairment on acute administration, and tolerance to these effects occurs on multiple dosing.

KEY WORDS: psychomotor performance; sedation; pharmacodynamics; pharmacokinetics; active metabolite; *N*-desmethyladinazolam.

INTRODUCTION

Adinazolam is a triazolobenzodiazepine which elicits antidepressant and anxiolytic activities in preclinical screens (1,2). The efficacy of immediate release (CT) adinazolam mesylate tablets has been assessed in the treatment of depression and panic disorder (3–5). Adinazolam is characterized by a short (≈2-hr) half-life (6,7), and >95% of an oral dose of adinazolam is metabolized to *N*-desmethyladinazolam (NDMAD) (8). After oral dosing with adinazolam, NDMAD achieves higher plasma concentrations than the parent compound and has a slightly longer plasma half-life (≈3–4 hr) (6,7). Following the administration of immediate-release (CT) adinazolam mesylate tablets three times daily to healthy volunteers, adinazolam and NDMAD pharmacokinetics were found to be linear from doses of 30 to 120 mg/day (Peng *et al.*, data on file, The Upjohn Company). Due to the short half-life of both adinazolam and NDMAD, their accumulation upon multiple dosing is minimal.

In man, the psychomotor performance and sedative effects observed following adinazolam administration appear to be mediated by NDMAD (8–10). This is most likely a consequence of the fact that, in *in vitro* binding assays, NDMAD has 25 times more affinity for central benzodiazepine receptors than does adinazolam (2,11). It is currently not known to what extent adinazolam and NDMAD contribute to the therapeutic effects seen on adinazolam administration.

A sustained-release (SR) formulation of adinazolam mesylate is currently under development for the treatment of panic disorder and generalized anxiety disorder. Initial results obtained in open-label pilot trials suggest that adinazolam mesylate SR tablets are effective in treating both disorders (12,13). Adinazolam mesylate SR tablets provide equivalent areas under the plasma concentration–time curve (AUC) for both adinazolam and NDMAD compared to the conventional tablet (14). However, maximal plasma concentrations of both adinazolam and NDMAD are lower and occur later with the SR tablet as compared to the CT. It is not currently known how the altered release pattern of adinazolam affects the time course of untoward and therapeutic effects observed following administration of adinazolam mesylate SR tablets. Therefore, the objectives of the studies described in this report were (i) to compare quantitatively the psychomotor performance decrements produced following administration of adinazolam mesylate SR and CT tablets and (ii) to compare the single- and multiple-dose pharmacokinetics and pharmacodynamics of adinazolam and *N*-desmethyladinazolam following the administration of SR and CT tablets. The doses of CT and SR tablets were chosen to reflect the highest multiple dose which may be therapeutically administered, 120 mg/day (4,5).

EXPERIMENTAL

Single Dose (Study 1). This trial was conducted at Harris Laboratories, Inc., Lincoln, Nebraska. The local Institutional Review Board approved the study, and informed consent was obtained from volunteers prior to their participation in the study. Fifteen healthy volunteers, with ages ranging from 19 to 49 years, were enrolled in this study. Subject weights ranged from 64.8 to 95.3 kg. Subjects were determined to be in good health by physical examination and standard clinical laboratory tests. Subjects received no known enzyme-inducing agents for 30 days prior to the study and no medication during the 7 days prior to study commencement. During the course of the study, subjects received no medication other than those specified in the protocol. Alcohol ingestion was prohibited for 2 days prior to and on study days.

Subjects received two 20-mg CT tablets inserted in gelatin capsules, two 30-mg SR tablets inserted in gelatin capsules, and placebo capsules according to a three-way cross-

[1] Clinical Pharmacokinetics Unit, 7215-24-2, The Upjohn Company, Kalamazoo, Michigan 49007.
[2] To whom correspondence should be addressed.

0724-8741/92/0400-0457$06.50/0

over design. Treatments were administered in a double-blind fashion. Seven days separated treatment phases. Subjects were required to fast for 12 hr prior to dosing until 4 hr after drug administration.

Serial venous blood samples were collected into heparinized vacutainers immediately prior to drug dosing and at 0.25, 0.50, 1.0, 1.5, 2.0, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, and 36 hr after each dose. Plasma was harvested from the samples after centrifugation and frozen until analyzed. Determinations of adinazolam and NDMAD in plasma were performed by HPLC (15).

The degree of sedation was assessed at each time a blood sample was drawn using a Nurse Rated Sedation Scale (NRSS) (16). Psychomotor performance was assessed using the digit-symbol substitution test (DSST) (17) and two card sorting tasks: sorting by fours (CS4) and by suits (CSSUIT). Card sorting tasks were performed using standard playing cards. The parameter measured by the DSST was the number of correct substitutions in 90 sec; the time required to complete the task was determined in the card sorting tests. These three tasks were administered three times on the evening before drug administration in each study phase, in order to minimize any learning effect with treatment phases. Performance tests were also administered 0.5 hr prior to dosing and at 1, 3, 6, and 8 hr after dosing.

Multiple Dose (Study 2). This study was conducted at the Arkansas Research Medical Testing Center, Little Rock. The protocol was approved by the local Institutional Review Board, and each subject provided written informed consent. A panel of 16 healthy male volunteers between 22 and 39 years of age entered and completed this study. Subject weights ranged from 63.5 to 97.5 kg. Subjects received the following treatments according to an open label, two-way crossover design within each dosing phase.

Single-dose phase: One adinazolam mesylate CT 10-mg and one CT 30-mg tablet (40 mg CT) or two adinazolam mesylate 30-mg tablets (60 mg SR).

Steady-state phase: One CT 10-mg tablet and one CT 30-mg tablet administered at 8 AM, 4 PM, and 12 AM (40 mg CT q 8 hr) or two SR 30-mg tablets administered at 8 AM and 8 PM (60 mg q 12 hr).

Single-dose treatments were administered on days 1 and 4 at 8 AM after a 12-hr fast. Immediately after the second single dose treatment, dosage was titrated up to 120 mg/day from day 5 to day 11. Subjects received SR and CT tablet multiple-dose phase treatments as outlined above on days 11–18. Standard meals were administered at 7 AM, 12 PM, and 6 PM. No washout occurred between multiple-dose regimens; subjects were immediately crossed over to the other formulation on day 15. Following the final dose on day 18, subjects were tapered off of the medication gradually from day 19 to day 30.

Serial venous blood samples were collected after dosing on days 1 and 4. For CT tablets during multiple dosing, blood samples were obtained prior to each dose on the first 3 days of the treatment period and at 0, 0.5, 1, 1.5, 2, 4, 6, and 8 hr after each dose on the last day of that period. For SR tablets, sampling times were at 8 AM and 8 PM on each of the first 3 days of the treatment period and at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hr after each dose on the last day of the study period. Plasma was harvested and frozen until analyzed.

Sedation was rated at each blood sampling time after single-dose administration and after the 8 AM dose on days 14 and 18. Psychomotor performance tasks were administered in three practice sessions on the evening of admission to the clinic. Performance tests were administered prior to dosing and at 2, 6, and 8 hr after the 8 AM dosing on days 1, 4, 14, and 18.

DATA ANALYSIS

Study 1. Noncompartmental techniques (18) were used in pharmacokinetic analyses. The terminal elimination rate constant (K) was determined by linear regression of the linear terminal portion of the log concentration–time profile. Area under the drug concentration–time curve (AUC) was determined by trapezoidal rule up to the last sampling time at which a quantifiable drug concentration was obtained and extrapolated to infinity. Apparent oral clearance (Cl_o) was calculated as dose/AUC. Maximal plasma concentrations (C_{max}) and the times at which they occurred (T_{max}) were determined graphically. Relative bioavailability (F) was calculated as the dose-corrected ratio of SR AUC-to-CT tablet AUC values. The molar ratio of NDMAD to adinazolam AUC values (NDMAD/AD) was calculated as

$$\frac{\text{NDMAD}}{\text{AD}} = \frac{\text{AUC}_{\text{NDMAD}} \cdot 351.87 \text{ g/mol}}{\text{AUC}_{\text{AD}} \cdot 337.87 \text{ g/mol}} \quad (1)$$

Differences in pharmacokinetic parameters among adinazolam doses were assessed using analysis of variance (ANOVA) with group, dose, and period as fixed effects and subject within group as a random effect. Due to the unbalanced nature of the pharmacokinetic portion the study, Type IV sums of squares were used to assess model effects in ANOVA (19).

Percentage decrements in psychomotor performance test scores were calculated relative to the zero-hour determination for each subject during each phase. Differences in performance decrements among treatments were assessed using repeated-measures ANOVA. Differences between individual treatments and times were assessed using least-squares means analysis. Maximal sedation scores were compared among treatments using the ANOVA model used for pharmacokinetic analyses.

Study 2. In addition to the parameters described above, under multiple-dose conditions, AUC was calculated by trapezoidal rule from 0 to 24 hr (AUC_{0-24}) on day 14 and day 18. Oral clearance (Cl_o) was calculated as dose/AUC or as daily dose/AUC_{0-24}. The steady-state fluctuation ratio (F_1) was calculated as (20)

$$F_1 = (C_{max} - C_{min})/C$$

where C is the mean steady-state plasma concentration over the dosing interval, described here as $AUC_{0-24}/24$. Steady-state conditions were confirmed by linear regression of the trough concentrations collected on days 11 to 13 and 15 to 17; a slope not significantly different from zero was taken as evidence of the achievement of steady state. Effects of treatment (SR or CT tablet) on pharmacokinetic parameters were assessed using ANOVA, with group, treatment, and period as fixed effects and subject within group as a random effect.

Differences between single- and multiple-dose parameters within treatments were assessed by paired t test.

Percentage decrements in psychomotor performance were calculated relative to the zero-hour determination during each phase. Formulation effects on performance decrements were assessed using repeated-measures ANOVA. Differences in maximal sedation score from 0 to 12 hr between formulations were assessed using ANOVA. Differences between single- and multiple-dose results were assessed by paired t test. Statistical analyses were performed using SAS (21).

RESULTS

Study 1. Plasma concentration–time profiles for adinazolam and NDMAD are depicted in Fig. 1. Pharmacokinetic parameters for adinazolam and NDMAD are summarized in Table I. Adinazolam dose-corrected AUC and oral clearance were similar following administration of SR and CT tablets; F for the SR tablets relative to the CT tablets was 0.914. Dose-corrected NDMAD AUC and NDMAD/AD were similar for SR and CT tablets. For both adinazolam and NDMAD, dose-corrected C_{max} was lower and $t_{1/2}$ was significantly longer for the SR tablets as compared to the CT tablets.

Psychomotor results are summarized in Table II. Significant decrements in DSST for the CT tablets compared to placebo were noted at each time after dosing; maximal effects were noted at 3 hr. For the SR tablets, significant decrements compared to placebo were observed at all times except 1 hr after dosing, with maximal decrements observed at 6 hr after dosing. Similar results were observed for both card sorting tasks, but maximal effects were observed at 1 hr after administration of the CT tablets.

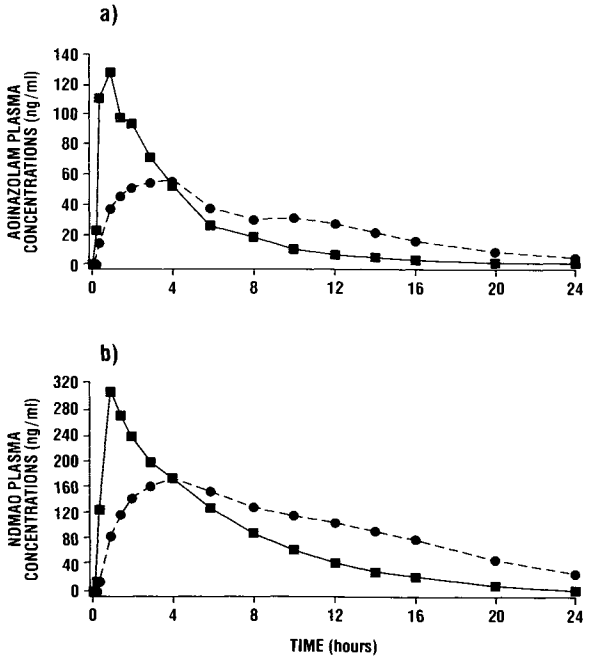

Fig. 1. Mean plasma adinazolam (a) and NDMAD (b) concentration–time profiles following the administration of 2 × 20-mg adinazolam mesylate CT tablets (■) and 2 × 30-mg adinazolam mesylate SR tablets (●) in 15 healthy male volunteers (Study 1).

Table I. Mean (±SD) Pharmacokinetic Parameters for Adinazolam and NDMAD in Plasma Following Administration of 2 × 20-mg Adinazolam Mesylate Tablets and 2 × 30-mg Adinazolam Mesylate SR Tablets to 15 Healthy Male Subjects (Study 1)

	Treatment			
	Adinazolam		NDMAD	
Parameter	40 mg CT	60 mg SR	40 mg CT	60 mg SR
AUC (ng hr/ml)	543 (372)	647 (210)	1826* (242)	2543* (538)
Dose corrected[a] AUC (ng hr/ml)	543 (372)	431 (140)	1826 (242)	1695 (359)
F[b]	—	0.914 (0.254)	—	—
Cl_o (L/hr)	73.8* (30.2)	80.1* (25.5)	—	—
C_{max} (ng/ml)	153* (70.2)	58.6* (20.8)	314* (88.1)	180* (45.0)
Dose corrected[a] C_{max} (ng/ml)	153* (70.2)	39.1* (13.8)	314* (88.1)	120* (30.0)
K (hr^{-1})	0.273* (0.092)	0.153* (0.029)	0.182* (0.040)	0.131* (0.023)
$t_{1/2}$ (hr)	3.01* (1.63)	4.73* (1.09)	4.06* (1.31)	5.43* (0.865)
T_{max} (hr)	0.817* (0.427)	2.87* (0.972)	1.43* (0.923)	3.73* (0.884)
NDMAD/AD	—	—	4.36 (1.66)	4.51 (1.83)

[a] Normalized to a 40-mg dose.
[b] Bioavailability relative to the CT tablet.
* Within drugs, parameters following CT and SR tablet administration are significantly different at $P < 0.05$ by ANOVA.

Mean sedation scores are depicted in Fig. 2. Maximal sedation occurred later with the SR tablets as compared to the CT tablets. Mean maximal sedation scores up to 12 hr after dosing were 2.47, 1.93, and 0.867 for the CT tablets, SR tablets, and placebo, respectively; these values were significantly different from one another at $P < 0.05$. Values from 14 to 24 hr were not included in the estimation of maximal sedation, since the increase in sedation during this period is probably indicative of normal sleep.

Study 2. Plasma adinazolam and NDMAD concentrations following multiple-dose administration of SR and CT tablets are shown in Fig. 3. Adinazolam and NDMAD pharmacokinetic parameters are summarized in Table III. No significant differences were observed between SR and CT tablets in dose-normalized AUC after single doses or in AUC_{0-24} after multiple doses for either compound. When AUC and AUC_{0-24} were normalized for the total dose administered, there were no significant differences among treatments for adinazolam or NDMAD. C_{max} for both compounds was higher for the CT tablets compared to the SR tablets, under both single- and multiple-dose conditions. Adinazolam and NDMAD T_{max} and half-life were significantly longer for SR tablets compared to CT tablets. Mean adinazolam C_{min} values were significantly higher for adina-

Table II. Mean (±SD) Baseline (0-hr) Scores and Percentage Decrements in Psychomotor Performance Test Scores Following Administration of 2 × 20-mg Adinazolam Mesylate CT Tablets, 2 × 30-mg Adinazolam Mesylate SR Tablets, and Placebo to 15 Healthy Male Subjects (Study 1)

Time (hr)	Treatment		
	40 mg CT	60 mg SR	Placebo
		DSST	
0.0	59.1	57.5	58.0
	(13.7)	(13.0)	(15.4)
1.0	28.9*,**	−0.88	−3.00
	(26.2)	(20.1)	(14.0)
3.0	32.9*,**	12.1*	−4.20
	(21.0)	(26.0)	(8.95)
6.0	14.9*	17.2*	−0.96
	(20.6)	(25.4)	(9.62)
8.0	9.83*	7.96*	−5.70
	(11.8)	(25.5)	(11.2)
		CSSUIT	
0.0	62.0	61.7	59.6
	(10.7)	(8.40)	(8.80)
1.0	50.2*,**	3.38	2.87
	(67.5)	(8.66)	(9.08)
3.0	26.2*	16.3	3.77
	(18.0)	(17.8)	(6.80)
6.0	17.1*	20.0*	0.823
	(18.3)	(27.3)	(6.65)
8.0	8.73	7.06	0.190
	(13.3)	(11.9)	(10.1)
		CS4	
0.0	75.8	76.6	70.1
	(14.4)	(10.5)	(9.56)
1.0	54.6*,**	1.02	−1.30
	(67.6)	(9.34)	(9.46)
3.0	30.7*	17.5	6.28
	(26.7)	(19.3)	(14.7)
6.0	17.0	20.6*	2.83
	(16.2)	(38.6)	(12.4)
8.0	3.92	4.32	−1.70
	(12.4)	(11.1)	(11.1)

* Significantly different from placebo by least square means analysis at $P < 0.05$.

** Significantly different from SR tablets by least square means analysis at $P < 0.05$.

zolam mesylate SR tablets as compared to CT tablets. F_1 for adinazolam was 2.63 ± 0.64 and 1.29 ± 0.24 for the CT and SR tablets, respectively. The average NDMAD C_{min} was 76 ± 15.9 for the SR tablets and 73.5 ± 23.3 for the CT tablets; this difference was not significant. F_1 for NDMAD was 1.61 ± 0.44 for the CT tablets and 1.01 ± 0.19 for the SR tablets.

Performance test results are summarized in Table IV. After single doses, significant differences between CT and SR tablets were observed at 2 hr for DSST and card sorting by fours. While decrements were higher at 2 hr for card sorting by suits after CT administration, the difference was not significant ($P = 0.1584$). On multiple dosing, performance decrements were significantly lower than those observed at 2 and 6 hr after single-dose administration, and no

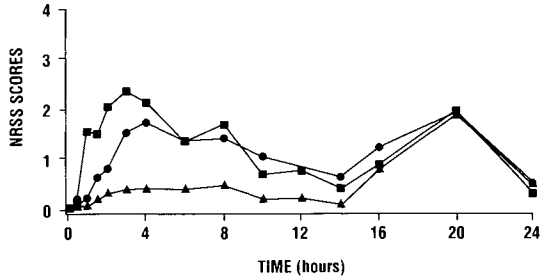

Fig. 2. Mean nurse rated sedation scores following the administration of 2 × 20-mg adinazolam mesylate CT tablets (■), 2 × 30-mg adinazolam mesylate SR tablets (●), and placebo (▲) in 15 healthy male volunteers (Study 1).

significant difference between SR and CT tablets in performance decrements was apparent.

Sedation score results are depicted in Fig. 4. Sedation scores were similar for the SR and CT tablet following single-dose administration. Sedation was significantly greater following single dose administration than following multiple-dose administration, where sedation was minimal.

DISCUSSION

Previous studies comparing the pharmacokinetics of adinazolam and NDMAD following the administration of adinazolam mesylate SR and CT tablets have been per-

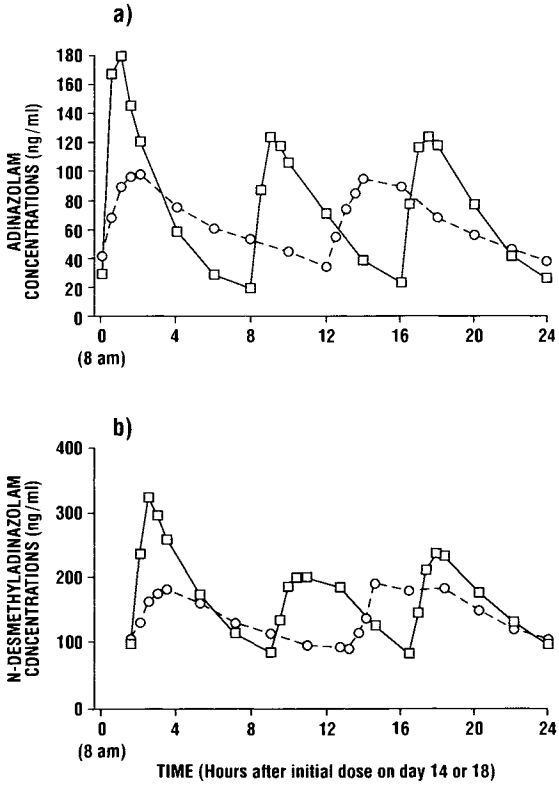

Fig. 3. Mean plasma adinazolam (a) and NDMAD (b) concentration–time profiles at steady state following the administration of 40 mg adinazolam mesylate as CT tablets every 8 hr (□) and 60 mg adinazolam mesylate as SR tablets every 12 hr (○) in 16 healthy male volunteers (Study 2).

Table III. Mean ± SD Adinazolam and NDMAD Pharmacokinetic Parameters Resulting from the Administration of Adinazolam Mesylate as Single Oral Doses of the CT Tablet and the SR Tablet and Multiple-Oral Doses of the CT Tablet and the SR Tablet to 16 Healthy Volunteers (Study 2)

Parameter	40-mg CT, single dose	60-mg SR, single dose	40-mg CT, q 8 hr	60-mg SR, q 12 h
		Adinazolam		
AUC[a] (ng × hr/ml)	570 ± 297*	882 ± 422*	1720 ± 628	1568 ± 726
AUC^{b}_{NORM} (ng × hr/ml)[b]	570 ± 297	592 ± 283	573 ± 209	523 ± 242
Cl_o (L/hr)	87.1 ± 43.9	79.0 ± 25.4	78.0 ± 24.7**	88.3 ± 28.9**
C_{max} (ng/ml)	151 ± 53.9*,***	73.4 ± 22.8*,****	199 ± 68.4**,***	111 ± 42.2**,****
C_{min} (ng/ml)			17.9 ± 13.2**	30.8 ± 20.1**
F_1			2.63 ± 0.636**	1.29 ± 0.238**
λ (hr^{-1})	0.309 ± 0.086*	0.130 ± 0.033*		
$t_{1/2}$ (hr)[c]	2.24	5.33		
T_{max} (hr)	1.03 ± 0.531*	2.44 ± 1.35*		
		NDMAD		
AUC[a] (ng × hr/ml)	1208 ± 247*,***	1860 ± 457*,****	3938 ± 605**,***	3354 ± 617**,****
AUC^{b}_{NORM} (ng × hr/ml)[b]	1208 ± 247	1248 ± 306	1313 ± 202	1118 ± 206
C_{max} (ng/ml)	206 ± 42.5*,***	122 ± 30.2*,****	331 ± 43.9**,***	217 ± 37.6**,****
C_{min} (ng/ml)			73.5 ± 23.3	76.0 ± 15.9
F_1			1.61 ± 0.439**	1.01 ± 0.187**
T_{max} (hr)	1.25 ± 0.483*	4.22 ± 3.11*		
λ (hr^{-1})	0.192 ± 0.054*	0.101 ± 0.025*		
$t_{1/2}$ (hr)[c]	3.61	6.86		

[a] AUC for single-dose treatments, AUC_{0-24} for multiple-dose treatments.
[b] Normalized to a 40-mg single dose of adinazolam mesylate.
[c] Harmonic mean.
* Difference between single-dose treatments is statistically significant (ANOVA, $P < 0.05$).
** Difference between multiple-dose treatments is statistically significant (ANOVA, $P < 0.05$).
*** Difference between single-dose (Treatment A) and multiple-dose (Treatment C) treatments is statistically significant (paired t test, $P < 0.05$).
**** Difference between single-dose (Treatment B) and multiple-dose (Treatment D) treatments is statistically significant (paired t test, $P < 0.05$).

formed at a dose of 15 mg (14). The objectives of the studies described here were to compare the pharmacokinetics and pharmacodynamics of adinazolam and NDMAD following administration of the highest single and multiple doses of SR and CT tablets to be administered in clinical efficacy studies.

The pharmacokinetic results observed in this study are similar to those reported previously (14). The pharmacokinetics of adinazolam and NDMAD following the administration of adinazolam mesylate CT tablets have been shown to be proportional to dose at doses of up to 60 mg (7). In this study, adinazolam dose-corrected AUC and Cl_o, as well as NDMAD dose-corrected AUC and the NDMAD/AD ratio, were not different between SR and CT treatments. These observations suggest that adinazolam and NDMAD kinetics are likewise proportional following single oral doses of adinazolam mesylate SR tablets of up to 60 mg.

Psychomotor performance tests were used in this experiment as a measure of the benzodiazepine-like behavioral effects of NDMAD. Treatment effects, as measured by these tests, may be obscured by a learning effect, as these tests are performed repeatedly. Practice tests were administered before the beginning of each phase in order to bring the subject to his maximum performance level prior to the administration of the test treatments and to minimize learning during the treatment day. This strategy was apparently successful, as mean baseline performance scores did not differ among treatments. In addition, the minimal changes in performance test scores elicited by placebo (<6% change from baseline scores for DSST, for example) suggest that a substantial learning effect did not occur during the study period.

Decrements in performance following the administration of adinazolam mesylate CT tablets were consistent with previous results (7). Performance decrements were less dramatic for the SR tablets; indeed, mean maximal decrements in DSST following the 60-mg SR tablets dose were similar to those previously observed for a 20-mg dose of the CT tablets (7). To put this in perspective to other triazolobenzodiazepines, the maximal decrement in DSST scores following SR tablet administration was similar to that produced by a 1-mg oral dose of alprazolam (22). Thus, the reduced peak NDMAD concentrations following SR tablet administration result in smaller sedation and psychomotor performance decrements for the SR tablets as compared to the CT tablets following single-dose administration.

The pharmacokinetic results from the single dose portion of Study 2 are similar to those from Study 1. The lack of difference in adinazolam AUC and oral clearance and NDMAD AUC between the SR and the CT tablets under multiple-dose conditions argues for the linearity of pharmacokinetics of both compounds after administration of the SR tablet at 120 mg/day, as the linearity of pharmacokinetics through this dose of the CT tablets has already been estab-

Table IV. Mean ± SD Baseline (0-hr) Psychomotor Performance Test Scores and Percentage Decrements in Psychomotor Performance Test Scores Produced by the Administration of Adinazolam Mesylate as Single Oral Doses of the CT Tablet and the SR Tablet and Multiple Oral Doses of the CT Tablet and SR Tablet to 16 Healthy Volunteers (Study 2).

Time (hr)	40-mg CT, single dose	60-mg SR, single dose	40-mg CT, q 8 hr	60-mg SR, q 12 hr
		DSST		
0	47.5 ± 10.6	47.6 ± 10.5	49.7 ± 10.3	52.0 ± 12.1
2	18.2 ± 22.8*	4.36 ± 14.8	−0.760 ± 11.6*	−4.50 ± 15.8
6	−0.580 ± 21.9	4.48 ± 25.9	−4.90 ± 13.5	−0.490 ± 15.0
8	−6.70 ± 15.5	−0.030 ± 20.0	−1.50 ± 13.5	1.39 ± 15.4
		CSSUIT		
0	39.6 ± 7.78	40.1 ± 13.2	39.1 ± 7.72	39.8 ± 9.31
2	37.1 ± 22.2*	26.7 ± 37.0**	7.64 ± 14.9*	3.62 ± 9.20**
6	18.4 ± 31.9*	14.2 ± 20.2**	−6.00 ± 19.4*	−3.10 ± 16.9**
8	8.72 ± 12.2*	8.97 ± 14.9	−2.20 ± 15.9*	−1.80 ± 14.2
		CS4		
0	64.7 ± 14.5	67.6 ± 18.8	65.2 ± 18.6	63.6 ± 16.0
2	26.4 ± 19.8*,***	10.7 ± 13.0**,***	−5.30 ± 17.7*	−6.10 ± 19.9**
6	10.9 ± 21.2*	12.9 ± 14.7**	−12.0 ± 14.9*	−6.50 ± 16.9**
8	−1.70 ± 10.2	1.63 ± 12.1	−5.80 ± 15.3	−4.40 ± 11.4

* Difference between single-dose (Treatment A) and multiple-dose (Treatment C) treatments is statistically significant (t test, $P < 0.05$).

** Difference between single-dose (Treatment B) and multiple-dose (Treatment D) treatments is statistically significant (t test, $P < 0.05$).

*** Difference between single-dose treatments is statistically significant (ANOVA, $P < 0.05$).

lished (Peng *et al.*, data on file, The Upjohn Company). The lack of difference in dose-normalized AUC for both adinazolam and NDMAD between single- and multiple-dose treatments also supports this hypothesis and confirms the predictability of multiple-dose behavior of these tablets.

Psychomotor test results for the single-dose portion of study 2 were similar to those for study 1, in that decrements were smaller for the SR tablets compared to the CT. However, mean performance decrements for both formulations were much lower in study 2 compared to study 1. This might have been due to the significant period effects observed for performance decrements, where decrements were substantially lower during the second period of the crossover. Period effects have not been observed in other pharmacodynamic studies with adinazolam (7–10), but the washout period in other studies was generally 7 days, whereas the washout period here was only 3 days. Previously, acute tolerance (within 1 dose) has not been observed following single doses of adinazolam or NDMAD (7,10). Therefore, it is unclear whether the period effect could have been due to tolerance occurring and not resolving during the 3-day washout period. Regardless of the period effects, the single-dose results are still consistent with reduced psychomotor effects following SR tablet administration.

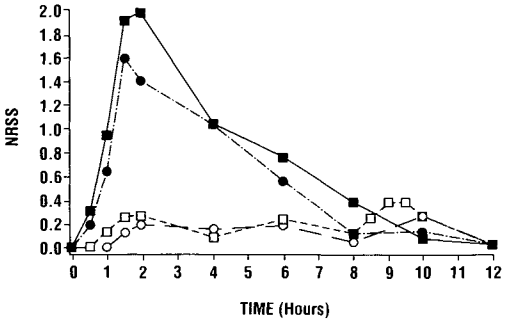

Fig. 4. Mean nurse-rated sedation scores following the administration of 40 mg adinazolam mesylate CT tablets as a single dose (■), 60 mg adinazolam mesylate SR tablets as a single dose (●), 40 mg adinazolam mesylate as CT tablets every 8 hr (□), and 60 mg adinazolam mesylate as SR tablets every 12 hr (○) in 16 healthy male volunteers. Results for the multiple-dose treatments are for the 12 hr following the 8 AM dose on days 14 and 18 (Study 2).

Comparison of the single- and multiple-dose psychomotor performance and sedation data show that tolerance occurs to these effects on multiple dosing, but without a placebo treatment, it is not possible to determine whether complete tolerance occurs or to assess the contribution of a learning effect to this apparent tolerance development. However, the insignificant performance decrements observed on multiple dosing, coupled with the lack of a substantial difference among single- and multiple-dose treatments in baseline scores, suggest that the contribution of a learning effect to the observed tolerance was minimal. Tolerance to the sedative effects of another sustained-release benzodiazepine formulation (alprazolam SR Tablets) has been shown to occur within 3 days of multiple dosing (23). It is clear that adinazolam is also subject to the development of tolerance, but the time frame for tolerance development remains a topic for future study.

In conclusion, adinazolam mesylate SR tablets provide an acceptable pharmacokinetic profile, based on the similarity the adinazolam and NDMAD steady-state AUC_{0-24} values for CT and SR tablets and lower maximal plasma con-

centrations and fluctuation ratios of both adinazolam and NDMAD for the SR tablets than for the CT tablets. On acute administration of the SR tablet, lower NDMAD C_{max} values result in smaller effects on psychomotor performance than observed for the CT tablet. At steady-state, tolerance to psychomotor and sedative effects occurs to similar extents for SR and CT tablet treatments.

REFERENCES

1. R. A. Lahti, V. H. Sethy, C. Barsuhn, and J. B. Hester. Pharmacological profile of the antidepressant adinazolam, a triazolobenzodiazepine. *Neuropharmacology* 22:1277–1282 (1983).
2. V. H. Sethy, R. J. Collins, and E. G. Daniels. Determination of biological activity of adinazolam and its metabolites. *J. Pharm. Pharmacol.* 36:546–548 (1984).
3. J. D. Amsterdam, M. Kaplan, L. Potter, L. Bloom, and K. Rickels. Adinazolam, a new triazolobenzodiazepine, and imipramine in the treatment of major depressive disorder. *Psychopharmacology* 88:484–488 (1986).
4. D. Dunner, J. Myers, A. Khan, D. Avery, D. Ishiki, and R. Pyke. Adinazolam—a new antidepressant: Findings of a placebo-controlled, double-blind study in outpatients with major depression. *J. Clin. Psychopharm.* 7:170–172 (1987).
5. R. E. Pyke and H. S. Greenberg. Double-blind comparison of alprazolam and adinazolam for panic and phobic disorders. *J. Clin. Psychopharmacol.* 9:15–21 (1989).
6. G. W. Peng, W. M. Todd, U. M. Rykert, R. P. Stryd, and R. E. Pyke. Dose proportionality of adinazolam mesylate (DERACYN). *Pharm. Res.* 3 (Suppl.):108s (1986).
7. J. C. Fleishaker and J. P. Phillips. Adinazolam pharmacokinetics and behavioral effects following administration of 20–60 mg oral doses of its mesylate salt in healthy volunteers. *Psychopharmacology* 99:34–39 (1989).
8. J. C. Fleishaker, H. L. Friedman, T. C. Smith, S. R. Pollock, C. M. Stubbs, and J. W. Bokros. Clinical pharmacology of adinazolam and N-desmethyladinazolam mesylate following single oral doses of 10 to 50 mg of each compound in healthy volunteers. *Clin. Pharmacol. Ther.* 48:652–664 (1990).
9. J. C. Fleishaker, H. L. Friedman, L. K. Hulst, and T. C. Smith. Kinetics/dynamics of adinazolam and its metabolite, N-desmethyladinazolam, after IV administration of each compound in man. *J. Clin. Pharmacol.* 30:833 (1990).
10. J. C. Fleishaker, T. C. Smith, H. L. Friedman, and J. P. Phillips. N-Desmethyladinazolam pharmacokinetics and behavioral effects following administration of 10 to 50 mg oral doses in healthy volunteers. *Psychopharmacology* 105:181–185 (1991).
11. V. H. Sethy, J. W. Francis, and J. S. Day. The effect of proadifen on the metabolism of adinazolam. *J. Pharm. Pharmacol.* 38:631–632 (1986).
12. D. V. Sheehan, A. B. Raj, K. Harnett-Sheehan, S. Soto, and C. P. Lewis. Adinazolam sustained release formulation in the treatment of generalized anxiety disorder. *J. Anxiety Disord.* 4:239–246 (1990).
13. D. V. Sheehan, A. B. Raj, K. Harnett-Sheehan, S. Soto, and C. P. Lewis. Adinazolam sustained release formulation in the treatment of panic disorder. *Irish J. Psychol. Med.* 7:124–128 (1990).
14. J. C. Fleishaker, J. P. Phillips, and H. S. H. Lau. Effect of food on the bioavailability of adinazolam from a sustained release formulation: Effect of meal timing and lack of dose dumping. *Biopharm. Drug. Disp.* 11:715–727 (1990).
15. J. C. Fleishaker, J. P. Phillips, T. C. Smith, and R. B. Smith. Multiple dose pharmacokinetics and pharmacodynamics of adinazolam in elderly subjects. *Pharm. Res.* 6:379–386 (1989).
16. R. B. Smith, P. D. Kroboth, and P. D. Varner. Pharmacodynamics of triazolam after intravenous administration. *J. Clin. Pharmacol.* 27:971–979 (1987).
17. D. Wechsler. *A Manual for the Wechsler Adult Intelligence Scale,* Psychological Corporation, New York, 1955.
18. M. Gibaldi and D. Perrier. *Pharmacokinetics,* 2nd ed., Marcell Dekker, New York, 1982.
19. G. A. Milliken and D. E. Johnson. *Analysis of Messy Data, Vol. I. Designed Experiments,* Van Nostrand Reinhold, New York, 1984.
20. J. P. Skelly. Issues and controversies involving controlled-release drug product studies. *Pharm. Int.* 7:280–286 (1986).
21. SAS Institute, Inc. *SAS User's Guide: Statistics, Version 5 Edition,* SAS Institute, Cary NC, 1985.
22. R. B. Smith, P. D. Kroboth, J. T. Vanderlugt, J. P. Phillips, and R. P. Juhl. Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. *Psychopharmacology* 84:452–456 (1984).
23. J. C. Fleishaker, J. P. Phillips, M. G. Eller, and R. B. Smith. Pharmacokinetics and pharmacodynamics of alprazolam following single and multiple oral doses of a sustained release formulation. *J. Clin. Pharmacol.* 29:543–549 (1989).