Pharmaceutical Research, Vol. 6, No. 5, 1989

Research Article

Multiple-Dose Pharmacokinetics and Pharmacodynamics of Adinazolam in Elderly Subjects

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Received July 11, 1988; accepted December 28, 1988

The pharmacokinetics and pharmacodynamics of adinazolam (AD) were evaluated in 21 elderly subjects (mean age, 69 ± 4 years) at four dose levels during a placebo-controlled, double-blind, dose escalation regimen in which the oral dose was varied from 10 to 60 mg daily, in divided doses. Fifteen subjects received adinazolam mesylate; six received placebo. Plasma samples collected during a single dosing interval in each dosing period (3 days) were assayed for adinazolam and monodesmethyl adinazolam (NDMAD) by high-performance liquid chromatography (HPLC). Urine samples were collected during a single interval during the 20- and 40-mg daily dose periods and assayed for NDMAD by HPLC. Pharmacologic effects of adinazolam were assessed using psychomotor performance tests and sedation ratings. Adinazolam pharmacokinetics were linear over the dosage range studied. Daily dose had no significant effect on dose-normalized AUC and C_{max} for AD. Dose-normalized NDMAD AUC values as well as β values were not significantly affected by the daily dose of adinazolam. The ratio NDMAD/AD was not substantially affected by the dose. Renal clearance of NDMAD for the 20- and 40-mg daily doses were 5.6 ± 2.1 and 5.5 ± 2.2 liters/hr, respectively, and did not correlate with creatinine clearance. Adinazolam and NDMAD did not substantially accumulate in elderly subjects, even upon multiple dosing at 8-hr intervals. The dosing regimens in this experiment appeared to be well tolerated in the elderly, as performance tests and sedation scores indicated no substantial dose-related effects of adinazolam on psychomotor performance.

KEY WORDS: adinazolam; mono-*N*-desmethyladinazolam; pharmacokinetics in elderly; psychomotor performance; pharmacodynamics; sedation.

INTRODUCTION

Adinazolam is a new triazolobenzodiazepine which, in preclinical screens (1) and clinical trials (2,3), appears to have antidepressant activity. In man, adinazolam is primarily metabolized via N-dealkylation by the hepatic mixed-function oxidase system (4). The major metabolite, mono-*N*-desmethyl-adinazolam (NDMAD) also possesses benzodiazepine-type activity (5) and achieves levels in plasma upon oral administration which are higher than parent drug levels (6).

The oxidative metabolism of a number of compounds has been found to be diminished in elderly subjects (7–9). In addition, diminished renal function in elderly patients may affect the elimination of adinazolam metabolites. These factors may increase the sensitivity of elderly patients to common side effects of benzodiazepines, such as sedation and decreases in psychomotor performance. To assist in the development of rational dosing guidelines for elderly patients, the pharmacokinetics and pharmacodynamics of adinazolam were assessed in a group of elderly subjects during a double-blind, placebo-controlled, dose escalation study. The dosages utilized in this study represent therapeutic regimens likely to be used clinically to treat depression.

MATERIALS AND METHODS

Subject Selection

The clinical portion of the study was conducted in the Kalamazoo Investigational Complex, Kalamazoo, Mich. The study was approved by the local Institutional Review Board, and all subjects gave written informed consent prior to participation in the study. Twenty-one (5 male, 16 female) healthy, nonobese volunteers over 65 years of age were selected for participation in this study. The subjects were determined to be in good health by physical examination, complete hematology (CBC with differential white blood-cell and platelet count), urinalysis, and blood chemistries. Subjects with any concurrent disease were accepted into the study only if the disease was controlled by drugs or other therapy. In addition, complete patient histories were obtained from these subjects. Subjects received no medication, other than those prescribed for control of disease states, for 7 days prior to starting the study. Several subjects were maintained on prescription medication for the control of disease processes; the medications are listed in Table I. Subjects were

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0724-8741/89/0500-0379$06.00/0

Table I. Concomitant Medications Administered to Subjects for Control of Existing Disease Conditions

Subject No.	Condition	Medication	Dose units/day	Adinazolam/placebo
7	Hypertension	Amiloride, 15 mg/ hydrochlorothiazide, 50 mg	1	A
	Thyroid deficiency	Liotrix-2	1	
12	Arthritis	Sulindac, 200 mg	2	A
15	Hypercholesterolemia	Colestipol, 5 g	1	P
17	Hypertension	Atenolol, 50 mg	2	A
18	Hypertension	Chlorothiazide, 250 mg/ reserpine, 0.125 mg	1	A
	Arthritis	Naproxen, 250 mg	2	
19	Hypertension	Spironolactone, 25 mg/ hydrochlorothiazide, 25 mg	1	A

confined to the clinic for the entire study period (23 days) and received no other central nervous system (CNS) drugs or ethanol during the study period.

Fifteen subjects (4 male, 11 female) were treated with the adinazolam mesylate according to the procedures outlined below. The remaining six subjects (one male, five female) received matching placebo. One adinazolam subject (No. 12) was dropped on study day 9 due to excessive sedation. The pharmacokinetic results reported here pertain to the 14 subjects (mean age, 69 ± 4 years) who received adinazolam and completed the study. The mean age of the placebo-treated subjects was 69 ± 2 years.

Drug Administration

Subjects received oral doses of 10- or 20-mg adinazolam mesylate tablets or matching placebo according to the following scheme.

Days 1–3: One 10-mg tablet qd (8 AM) (10 mg/day).
Days 4–6: One 10-mg tablet q12h (8 AM, 8 PM) (20 mg/day).
Days 6–9: One 20-mg tablet q12h (8 AM, 8 PM) (40 mg/day).
Days 10–12: One 20-mg tablet q8h (8 AM, 4 PM, 12 AM) (60 mg/day).
Days 13–15: One 20-mg tablet q12h (8 AM, 8 PM) (40 mg/day).
Days 16–18: One 10-mg tablet q12h (8 AM, 8 PM) (20 mg/day).
Days 19–21: One 10-mg tablet qd (8 AM) (10 mg/day).

Standard meals were administered at 7 AM, 12 PM, and 6 PM.

Blood samples were collected at time zero (0) and then at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hr after the administration of the morning dose on days 1, 6, 9, and 13. Samples for trough levels were drawn before each dose on days 1–13 and thereafter drawn on days 14, 17, and 20, before the morning dose only. Blood samples were drawn into heparinized vacutainers, the samples were centrifuged, and plasma was harvested and frozen as soon as possible. Plasma was stored frozen until assayed.

Complete 12-hr urine collections were made during the first dosing intervals on days 6 and 9. The total urine volume was recorded, and aliquots were frozen until assayed for NDMAD.

Drug Analysis

Adinazolam and NDMAD plasma concentrations were determined by a high-performance liquid chromatographic (HPLC) method (manuscript in preparation). Briefly, 75 μl of internal standard (U-53,425E, The Upjohn Company) was added to 1 ml of plasma sample or standard. The sample was acidified with 1 ml 2.0 *M* HCl and extracted with 5 ml ethylacetate:petroleum ether mixture (2:1, v/v). The organic layer was separated and discarded. The remaining aqueous phase was basified with 4 *M* NaOH and extracted with 5 ml butylchloride. The organic phase was then removed and evaporated to dryness at 40°C under nitrogen. The residue was reconstituted in 150 μl mobile phase (0.06 *M* ammonium phosphate buffer:acetonitrile:methanol, 65:25:10, v/v/v), and injected onto the chromatograph. A 10-μm, C-18, reversed-phase 30 cm × 3.9 mm μBondapak column (Waters Associates) was used; the mobile phase flow rate was 1.5 ml/min. UV detection at 225 mm using a LC-95 UV detector (Perkin–Elmer) was used for quantitation of drug levels in the effluent. Standard curves for adinazolam were linear over 5–100 and 100–400 ng/ml. Standard curves for NDMAD were linear over the same region. The intra- and interday coefficients of variation were less than 10%.

NDMAD levels in urine were also determined by HPLC using a chromatographic system and extraction procedure similar to those used in plasma analyses, except that 1.5% isopropanol was included in the mobile phase. Standard curves were linear from 5 to 100 and from 100 to 400 ng/ml. Within- and between-day coefficients of variation were less than 6%.

Plasma protein binding of adinazolam and NDMAD could not be assessed due to the lack of sufficient assay sensitivity and the unavailability of radiolabeled compounds.

Psychomotor Performance Assessment

A Nurse-Rated Sedation Scale (NRSS) (10,11) was used to assess sedation due to adinazolam. Sedation was scored by a blinded observer at each blood sampling time. The sedation ratings were (1) no sedation, (2) calm but not asleep, (3) asleep but easily aroused, (4) asleep and not easily aroused, and (5) unable to communicate.

The effect of adinazolam on short-term memory was assessed using the Randt Memory Test (12) at 0, 2, 4, 6, and 9 hr after drug administration on days 1, 3, 6, 9, and 13. Short-term memory was also evaluated on a single occasion at the end of the study. The parameter evaluated was the number of correctly identified images.

Psychomotor performance was assessed using the digit

symbol substitution test (DSST) (13). Subjects were administered three practice tests on the evening before the first adinazolam dose and were administered different but equivalent tests throughout the study. The parameter measured was the number of correct responses in 90 sec. Two other tasks, card sorting by fours and card sorting by suit, were also used to measure psychomotor performance. In these tests, the time to complete the task was determined. Both DSST and card sorting were performed at the same time points as the memory tests.

Data Analysis

Pharmacokinetic parameters for the dosing intervals examined on days 1, 6, 9, and 13 were calculated using noncompartmental techniques (14). Terminal disposition rate constants (β) were determined from linear least-squares regression of the terminal portion of the log concentration–time profile. For drug and metabolite on day 1, the area under the plasma concentration–time profile to the last time point (AUC_t) was estimated by trapezoidal rule. The total area under the plasma concentration–time curve (AUC) was calculated by adding AUC_t and the residual area calculated by C_t/β, where C_t is the plasma concentration at the last time point at which the concentration may be quantified. AUC values for days 6, 9, and 13 were estimated by trapezoidal rule from time = 0 to time = τ, where τ is the length of the dosing interval. Assuming linear kinetics, these values represent the total AUC for a single dose (14). Apparent oral clearance (assuming 100% drug absorption) for adinazolam was calculated as $Cl_o = D/\text{AUC}$, where D is the oral dose. The apparent volume of distribution of adinazolam (Vd/F) was calculated as $V_d/F = Cl_o/\beta$, where F represents the fractional bioavailability of adinazolam. The terminal half-life ($t_{1/2}$) was calculated as $0.693/\beta$. The maximum plasma concentrations (C_{max}) and the times at which they occurred relative to the dose (T_{max}) were determined from the plasma concentration–time profile.

In addition to the parameters listed above, the steady-state metabolite-to-parent average concentration ratio was calculated as

$$\frac{\text{NDMAD}}{\text{AD}} = \frac{C_{ss}\text{NDMAD}}{C_{ss}\text{AD}} = \frac{\text{AUC}_{\text{NDMAD}}}{\text{AUC}_{\text{AD}}} \times \frac{351.87}{337.87} \quad (1)$$

which represents the ratio of molar concentrations.

For the dosing intervals of interest on days 6 and 9, the total amoung of monodesmethyladinazolam excreted in the urine (Ae) was determined by multiplying NDMAD urine concentrations by the urine volume for the collection interval. The renal clearance of NDMAD (Cl_{RM}), was calculated as

$$Cl_{RM} = \frac{Ae_{\text{NDMAD}}}{\text{AUC}_{\text{NDMAD}}} \quad (2)$$

where M refers to the NDMAD.

Statistical analyses were performed using SAS (15). Differences in pharmacokinetic parameters among the daily dosing regimens were assessed by analysis of variance (ANOVA), with daily dose and subject as model effects. Comparisons between parameter means among individual dosing regimens were then performed using Duncan's multiple-range test. Differences in Ae and Cl_{RM} between the 20- and the 40-mg daily doses administered on days 6 and 9 were assessed using a paired t test.

The effects of dosing regimen on sedation, memory, and psychomotor performance were assessed by a paired t test comparing performance scores at each time point with baseline scores. Comparisons between drug-treated and placebo groups were also made at each time point using unpaired t tests. Repeated-measures analysis of covariance (ANOCV) was also used to assess differences in psychomotor performance and sedation between treatment groups. The factors used in this analysis were treatment, subject nested within treatment, time after initial dose, and a treatment–time interaction. The baseline value for each performance test was the covariate.

RESULTS

Adinazolam plasma concentrations after 10-mg doses on day 1 (10 mg qd) and day 6 (10 mg q12h) were low and variable. After 4 hr in some of the patients, plasma adinazolam concentrations were below detection limits. Therefore, the estimates of β, $t_{1/2}$, and V_d/F were less reliable than those obtained after a 20-mg dose on day 9 (20 mg q12h) and day 13 (20 mg q8h). In addition, Cl_o values for the 10-mg daily dose may also have been affected by the low and variable adinazolam levels. The values for these parameters, however, have been included in the subsequent analyses.

A representative concentration–time profile for adinazolam in plasma from a single subject is shown in Fig. 1. Pharmacokinetic parameters estimated for adinazolam are summarized in Table II. No significant differences were found among the dose-normalized AUC values ($P = 0.1934$). Cl_o and clearance normalized for body weight (Cl_{ow}) were significantly affected by dose ($P = 0.0302$ and $P = 0.0306$, respectively), with the highest clearance occurring with 10 mg qd (54.8 ± 22.3 liters/hr). As with AUC, the C_{max} after 20-mg doses (q12h and q8h) was approximatley twice that for the 10-mg doses. Dose-normalized C_{max} values showed a trend toward a dose effect ($P = 0.0532$), with the C_{max} after 20 mg q12h (43.4 ± 17.1 mg/ml) being the lowest value. T_{max} was not affected by the dose administered ($P = 0.3376$). Significant dose effects were observed for β, V_d/F, and apparent volume of distribution corrected for body weight (V_{dw}/F) ($P < 0.001$ in all three cases). The values for these parameters were not significantly different between the 20-mg q8h and the 20-mg q12h regimens (Table II). The mean terminal half-lives after the 20-mg doses were 3.85 and 3.69 hr, respectively.

A representative plot of NDMAD plasma concentration versus time in a single individual is shown in Fig. 2. Pharmacokinetic parameters for NDMAD are summarized in Table III. No significant dose effects were observed for dose-normalized AUC ($P = 0.8981$). C_{max}, whether reported as raw C_{max} or dose-normalized C_{max}, was significantly affected by dose ($P < 0.001$ in both cases). T_{max} was unaffected by the daily dose administered ($P = 0.2735$). No significant effect of dose on β for NDMAD was observed ($P = 0.3126$). The metabolite-to-parent ratio, NDMAD/AD, was significantly affected by the dose ($P = 0.0286$) with the ratio

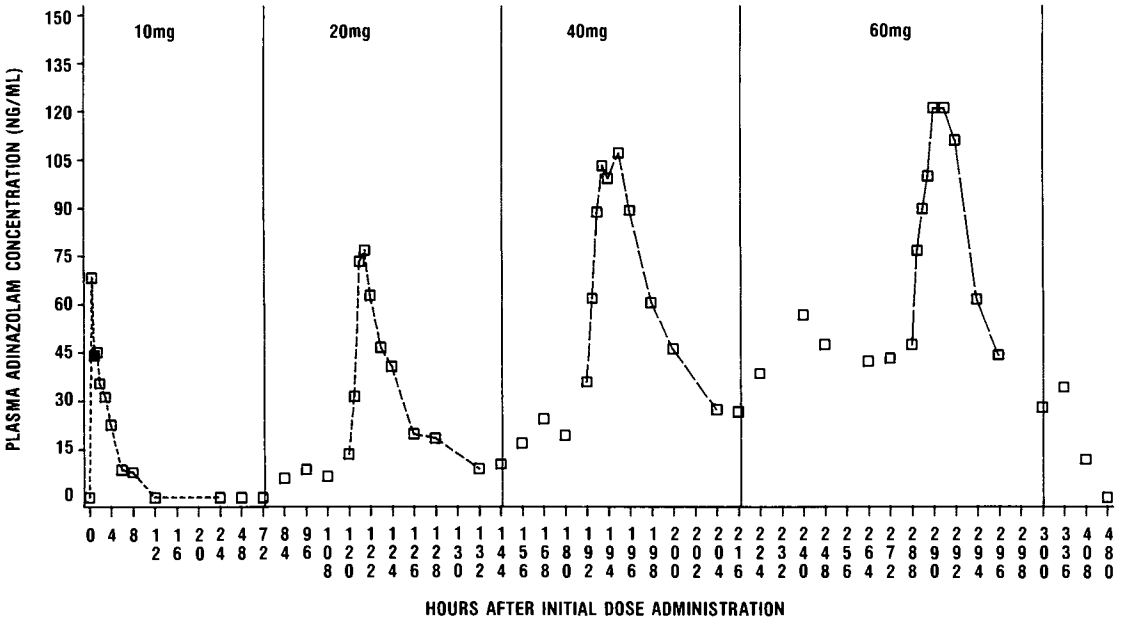

Fig. 1. Plot of adinazolam concentration versus time in elderly subject No. 8 following oral dosing with adinazolam mesylate according to the scheme given in Materials and Methods. Vertical reference lines represent changes in daily dosage regimens. (Note differences in time axis spacing.) Regions where points are joined by lines represent dosing intervals for which kinetic parameters were determined.

after the 10-mg qd dose being significantly different from that during the 20-mg q8h regimen (Table II). Cl_{RM} was not significantly different for the 10- and 20-mg doses given q12h ($P = 0.7477$). *Ae* was proportional to the adinazolam dose administered and represented approximately 50% of the administered dose.

The effects of adinazolam on psychomotor performance were quite variable. Figure 3 depicts DSST scores in treatment and placebo groups. DSST scores generally increased throughout the drug treatment period in both drug-treated and placebo groups, indicating that a learning process was occurring during the course of the study. In general, DSST scores were lower for the drug-treated group. However, the difference between the two groups in DSST, when expressed as percentage change from baseline, was significant only at 2, 6, 194, and 290 hr into the study. In addition, repeated-measures ANOCV revealed only a borderline significant ($P = 0.0752$) treatment effect on DSST. A significant time effect ($P < 0.0001$) and treatment–time interaction ($P = 0.0049$) were also observed. No significant treatment effects on memory were evident by ANOCV ($P = 0.209$). When expressed as raw scores (number correct), no significant differences in short-term memory were evident at any time after dosing. However, when expressed as percentage dif-

Table II. Plasma Pharmacokinetic Parameters for Adinazolam (Mean ± SD)

	Elderly			
Daily dose (mg)	10 (10 mg qd)	20 (10 mg q12h)	40 (20 mg q12h)	60 (20 mg q8h)
AUC (ng hr/ml)	183 ± 126*	203 ± 122*	417 ± 226	431 ± 218
Dose-normalized AUC (ng hr/ml)[a]	183 ± 126	203 ± 122	209 ± 113	216 ± 109
Cl_o (liters/hr)	54.8 ± 22.3**	50.8 ± 24.4	49.2 ± 25.1	46.6 ± 23.5
Cl_{ow} (liters/hr/kg)	0.79 ± 0.36*	0.73 ± 0.39	0.71 ± 0.68	0.68 ± 0.37
C_{max} (ng/ml)	51.7 ± 20.5*	48.1 ± 17.6*	86.9 ± 34.1**	104 ± 41.1
Dose-normalized C_{max} (ng/ml)[a]	51.7 ± 20.5	48.1 ± 17.6	43.4 ± 17.1	52.2 ± 20.6
V_d/F (liters)	164 ± 29.2*	191 ± 73.7*	265 ± 85.2	242 ± 85.6
V_{dw}/F (liters/kg)	2.34 ± 0.50*	2.70 ± 0.96*	3.79 ± 1.35	3.48 ± 1.35
T_{max} (hr)	1.18 ± 0.46	1.43 ± 0.58	1.57 ± 0.80	1.36 ± 0.60
β (hr^{-1})	0.343 ± 0.143***	0.276 ± 0.128*	0.180 ± 0.056	0.188 ± 0.057
$t_{1/2}$ (hr)[b]	2.02	2.51	3.85	3.69

[a] Normalized to a 10-mg dose.

[b] Harmonic mean.

* Significantly different from both 40- and 60-mg daily doses by Duncan's multiple-range test ($P < 0.05$).

** Significantly different from the 60-mg daily dose by Duncan's multiple-range test ($P < 0.05$).

*** Significantly different from the 20-, 40-, and 60-mg daily doses by Duncan's multiple-range test ($P < 0.05$).

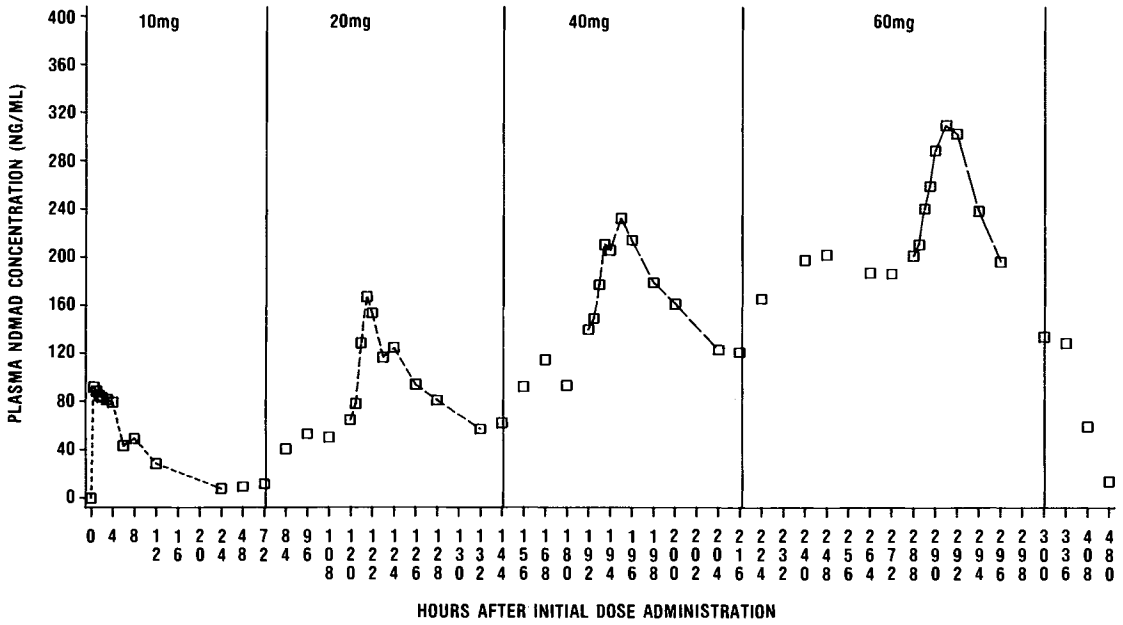

Fig. 2. Plot of *N*-desmethyladinazolam (NDMAD) versus time in elderly subject No. 8 following oral administration of adinazolam according to the scheme given in Materials and Methods. Vertical reference lines represent changes in daily dosage regimens. (Note differences in time axis spacing.) Regions where points are joined by lines represent dosing intervals for which kinetic parameters were determined.

ferences compared to baseline (zero-hour) scores, significant between-group differences in memory were noted at 2, 57, 192, 290, and 297 hr. No significant differences in card-sorting scores between groups were evident by repeated-measures ANOCV ($P = 0.2418$ and $P = 0.1965$ for card sorting by fours and suit, respectively).

Sedation scores were assessed in both placebo and adinazolam treatment groups. A systematic difference in the scores from subjects 15–21, as compared to the first 13 subjects, was noted; the data from these seven subjects were therefore excluded from analysis. Sedation scores from the first 13 subjects are shown in Fig. 4. The highest sedation score reported in these subjects (9 adinazolam, 4 placebo) was 3: asleep but easily aroused. While sedation scores significantly elevated from baseline levels were observed at several time points in the dosing intervals, the sedation scores were poorly related to the plasma adinazolam concentration; the slope of the regression line of sedation score versus plasma adinazolam concentration was borderline significant ($P = 0.0571$ and $r^2 = 0.0071$). In addition, differences in mean sedation scores between the two groups were significant only at 195 and 290 hr. Repeated-measures

Table III. Plasma Pharmacokinetic Parameters for *N*-Desmethyladinazolam (Mean ± SD)

	Elderly			
Daily dose (mg)	10 (10 mg qd)	20 (10 mg q12h)	40 (20 mg q12h)	60 (20 mg q8h)
AUC (ng hr/ml)	720 ± 145*	725 ± 176*	1433 ± 316	1420 ± 341
Dose-normalized AUC (ng hr/ml)[a]	720 ± 145	725 ± 176	717 ± 158	710 ± 170
C_{max} (ng/ml)	104 ± 19.2*	119 ± 24.7*	225 ± 52.6**	267 ± 70.0
Dose-normalized C_{max} (ng/ml)[a]	104 ± 19.2***	119 ± 24.7**	113 ± 26.3**	134 ± 35.0
T_{max} (hr)	1.57 ± 0.65	1.96 ± 0.63	1.96 ± 0.95	2.04 ± 0.84
β (hr^{-1})	0.134 ± 0.023	0.146 ± 0.034	0.133 ± 0.027	0.142 ± 0.028
$t_{1/2}$ (hr)[b]	5.17	4.75	5.21	4.88
NDMAD/AD (*M/M*)	5.04 ± 1.86**	4.64 ± 2.04	4.52 ± 2.25	4.24 ± 2.08
Ae (mg)	—	3.8 ± 1.1****	7.3 ± 2.2****	—
Ae (% of dose)	—	50.7 ± 14.7	48.4 ± 14.7	—
Cl_{RM} (liters/hr)	—	5.66 ± 2.06	5.50 ± 2.24	—

[a] Normalized to a 10-mg dose.

[b] Harmonic mean.

* Significantly different from both 40- and 60-mg daily doses by Duncan's multiple-range test ($P < 0.05$).

** Significantly different from the 60-mg daily dose by Duncan's multiple-range test ($P < 0.05$).

*** Significantly different from the 20- and 60-mg daily dose by Duncan's multiple-range test ($P < 0.05$).

**** Values are significantly different at $P < 0.05$ by paired *t* test.

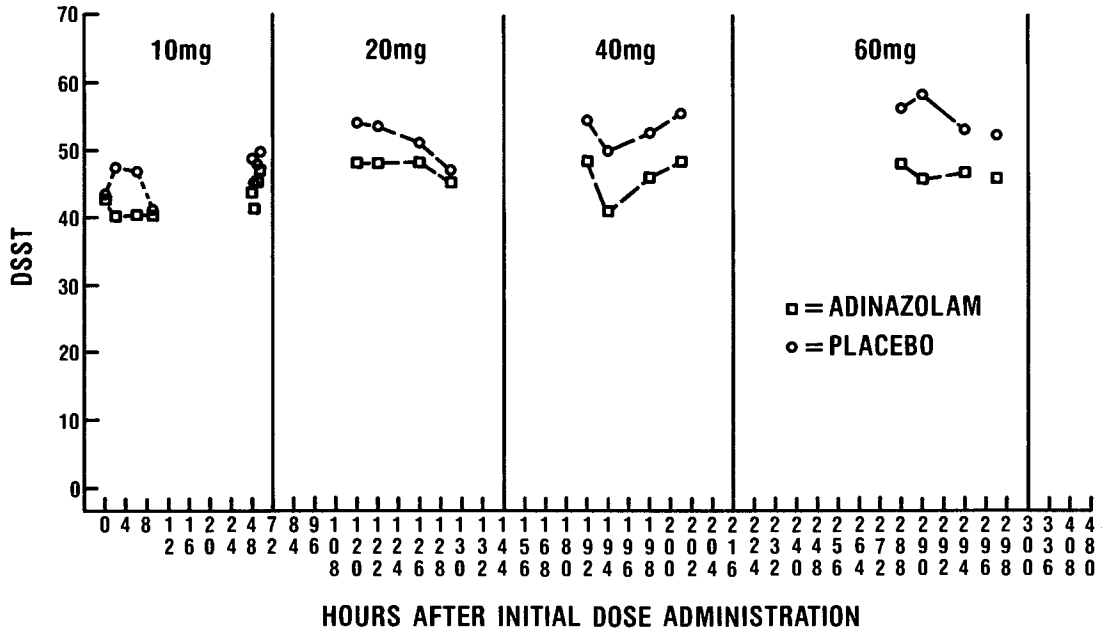

Fig. 3. Plot of DSST score versus time in nine elderly subjects following oral administration of adinazolam (N = 14) and placebo (N = 6) according to the scheme given in Materials and Methods. Vertical reference lines represent changes in daily dosage regimens. (Note nonuniform time axis spacing.)

ANOVA revealed no significant treatment effects on sedation (P = 0.2168).

DISCUSSION

This study was designed to examine the pharmacokinetics and pharmacodynamics of adinazolam and NDMAD following administration of adinazolam according to dosage regimens which would likely be used clinically in elderly subjects. The psychomotor, sedative, and amnestic effects are important, since they may limit the dose of adinazolam which may be safely administered. The interpretation of the results may be complicated by the fact that elderly depressed patients were not used in the study. However, the measurements of adinazolam's sedative amnestic, and psychomotor effects in the elderly provides a starting point for dosage regimen adjustment.

Plots of adinazolam and NDMAD concentrations versus time for an individual subject are shown in Figs. 1 and 2. The curves indicate that the accumulation on multiple dosing of adinazolam and NDMAD was not extensive in elderly subjects. This was supported by the lack of dosing regimen effect on the dose-normalized C_{max} for adinazolam; the dose-normalized C_{max} for NDMAD was only 19% higher when 20 mg was administered q8h as opposed to q12h. The accumulation factors (R) based on C_{max} values were 1.11 and 1.21 for adinazolam and NDMAD, respectively, for the 20-mg q8h regimen. As previously stated, these results are expected, since, if the drug doses are administered in the postdistributive phase, R can be estimated as (14)

$$R = \frac{C_{(ss)}\text{min}}{C_{(1)}\text{min}} = \frac{1}{1 - e^{-\beta\tau}} \qquad (3)$$

where C_{ss}(min) is the trough concentration at steady state and $C_{(1)}$min is the trough concentration after the first dose. For adinazolam and NDMAD the theoretical R values are 1.29 and 1.47, calculated from β and τ for the 20-mg q8h regimen. Thus, in the elderly, the extensive accumulation of drug and metabolite on multiple dosing should not occur with adinazolam as it does with longer-half-life benzodiazepines (16).

The results of the study also were indicative of linear adinazolam kinetics over the range of daily doses studied. Dose-normalized AUC values were constant over the range of doses studied, although Cl_o and Cl_{ow} for the 10-mg qd dose were significantly different from those for the 20-mg doses (q12h and 8h). This discrepancy, as well as differences in β among the lower doses, was probably due to the variability of the concentration time data for the 10-mg (qd and q12h) doses. In other words, the differences observed in Cl_o, Cl_{ow}, β, V_d/F, and V_{dw}/F were probably due to variability in the concentration–time data for the lower doses, rather than a real change in these parameters. Thus, the best estimates of all pharmacokinetic parameters determined in this study may be obtained from data for the 20-mg q12h and q8h dosing regimens. Renal clearance for adinazolam was not assessed in this study since the percentage of the dose which is excreted in the urine as intact adinazolam is <2% (unpublished information, The Upjohn Company).

The data for NDMAD were also indicative of linear kinetics. This was supported by the lack of dose effects on the dose-normalized AUC and β. The NDMAD/AD ratio was also constant over the 10-mg q12h, 20-mg q12h, and 20-mg q8h regimens; the high value for the 10-mg qd dose was probably due to the variability in AUC for adinazolam, which was previously discussed. Thus, the kinetics of NDMAD appear to be dose independent for the range of doses studied. These results, in addition to the observed

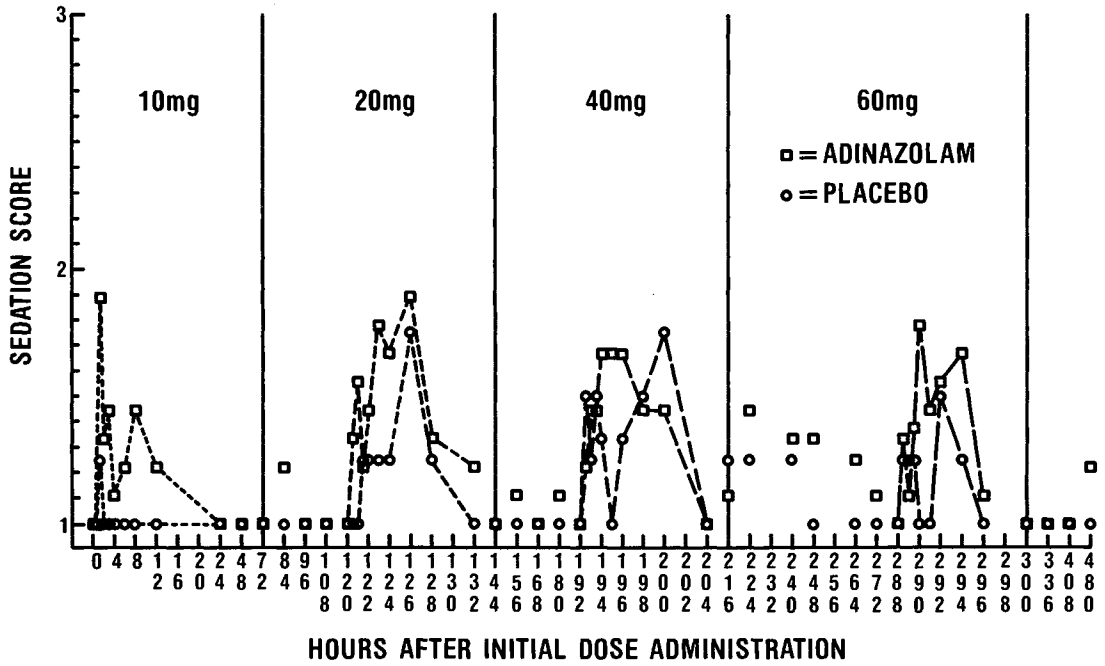

Fig. 4. Plot of mean sedation score versus time in nine elderly subjects following oral administration of adinazolam (N = 9) and placebo (N = 4) according to the scheme given in Materials and Methods. Vertical reference lines represent changes in daily dosage regimens. (Note nonuniform time axis spacing.) The sedation scores represent (1) no sedation, (2) calm but not asleep, and (3) asleep but easily aroused; sedation ratings 4 and 5 are not depicted on the Y axis. Regions where points are joined by lines represent dosing intervals for which kinetic parameters were determined.

dose linearity of adinazolam pharmacokinetics, agree with earlier results demonstrating the linearity of adinazolam and NDMAD pharmacokinetics following single oral doses of 10–40 mg adinazolam mesylate in young normal volunteers (17). However, nonlinear behavior at higher doses may be possible (18).

The renal clearance of NDMAD was determined over one dosing interval on day 6 (10 mg q12h) and day 9 (20 mg q12h). Cl_{RM} values were not significantly affected by dose, indicating that renal clearance of NDMAD was dose independent in this region. Cl_{RM} had a mean value of 94.3 ± 34.3 ml/min on day 6 (10 mg q12h). Creatinine clearance values were determined in these subjects in a prestudy screen, on study day 13, and on study day 21. The mean creatinine clearance value for day 13 was 73.19 ± 25.85 ml/min. The value for Cl_{RM} thus indicates that in elderly patients, both glomerular filtration and, to some extent, tubular secretion are involved in the renal elimination of NDMAD. This observation is also supported by the lack of correlation of Cl_{RM} with creatinine clearance (P = 2995, r^2 = 0.0892). The protein binding of the metabolite was not determined in this study; the relative contributions of the two pathways cannot then be determined.

The pharmacokinetics of adinazolam in young, male subjects have been previously studied by Wagner *et al.* (18). In that study, mean AUC values, normalized for a 10-mg dose, were 310 and 1048 ng hr/ml for adinazolam and NDMAD, respectively. These values were higher than the AUC values observed in the present study for adinazolam and NDMAD (203 and 725 ng hr/ml, respectively, for the 10-mg bid regimen). The NDMAD/AD ratio was higher in young subjects (5.79) than in the elderly subjects (4.64). The data for the eight young volunteers, however, were characterized by a large degree of intersubject variability (18). Different assay methodologies were used in these studies, which may also be responsible for the differences in these parameters between studies. The importance of any age-related difference in the pharmacokinetics of adinazolam needs to be judged in relation to its pharmacodynamic effects.

Substantial decrements in psychomotor performance were not evident during the course of adinazolam administration. This observation was probably due to the administration of rather low individual doses (10 and 20 mg) of adinazolam and the lack of substantial accumulation of adinazolam and NDMAD upon multiple dosing. DSST has been used to assess psychomotor performance following the administration of alprazolam (10,11) and has performed well in demonstrating decrements in psychomotor performance after the administration of alprazolam (10) and in demonstrating the development of tolerance to psychomotor effects of alprazolam (11). A learning effect was apparent in this study and has been observed previously in studies with alprazolam (10). DSST results would thus tend to underestimate the decrease in psychomotor performance due to adinazolam. However, the inclusion of a placebo group minimizes this effect. The difference in DSST between the groups was generally not significant and the difference in mean raw DSST scores between the groups was less than 20%. In addition, card sorting tests, which we have previously used to assess psychomotor performance following triazolam administration (19), revealed little difference in performance between

the groups. Thus, psychomotor performance did not appear to be substantially decreased in the elderly by the doses of adinazolam used in this study.

Memory tests revealed no differences between the groups in absolute recall but did detect some decrements in short-term memory (as compared to baseline) in the treated group. These decrements were small (<16%) and did not appear to be dose related. These results indicate that adinazolam has little effect on memory in the doses administered; the results are in contrast to the marked amnestic effects observed with other benzodiazepines (20).

The Nurse-Rated Sedation Scale (NRSS) has been used in previous studies to assess the sedative effects of alprazolam (10,11) and had been found to perform better than patient self-rating methods, such as the Stanford Sleepiness Scale (10,21). Mean sedation scores were significantly different from baseline at several time points following adinazolam administration in each dosing interval studied, as shown in Fig. 4. However, mean sedation scores exhibited significant between group differences at only two time points. The highest sedation score observed in this study was 3 (asleep but easily aroused). The NRSS does depend on consistent rating by a blinded observer. Therefore, sedation scores were analyzed only for subjects 1–14; systematic differences in the sedation scores from subjects 15–21 (4 adinazolam, 2 placebo), due to a different observer being used, resulted in these data being excluded from data analysis. Subject 12 was dropped from the study due to excessive sedation on study day 8. Up to this time point, subject 12 exhibited the highest plasma levels of adinazolam and NDMAD. Thus the results show that 10- and 20-mg doses of adinazolam administered up to three times daily did not generally result in excessive sedation in elderly subjects, due to the minimal accumulation of the drug upon multiple dosing.

The bulk of the psychomotor performance results obtained in this study was obtained at steady state, with only the first 10-mg dose constituting a test in drug naive patient. It is well known that chronic tolerance to the psychomotor effects of benzodiazepines occurs (11). It is therefore possible that significant performance decrements might be observed in elderly patients receiving an initial dose of greater then 10 mg adinazolam mesylate; patients started on higher doses may require increased observation.

The results of this study demonstrate that the pharmacokinetics of adinazolam and NDMAD are linear over the range of daily doses studied in elderly subjects. Due to the short half-lives of both adinazolam and NDMAD, the accumulation of both species upon multiple dosing was minimal. Adinazolam, at the doses used in this study, elicited no substantial impairment of psychomotor performance or short-term memory in the elderly. Sedation scores indicated that sedative effects were generally mild and did not appear to be dose related. One subject was dropped from the study because of excessive sedation, suggesting that there may be elderly individuals who are more sensitive to the sedative effects of benzodiazepines. In general, however, adinazolam was well tolerated in elderly subjects taking up to 60 mg/day in divided doses.

ACKNOWLEDGMENTS

We wish to thank Betty Davis, Judy DeVoe, and other members of the staff of the Kalamazoo Clinical Investigational Complex for their many contributions to the conduct of this study.

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