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Research Article

Extent and Variability of the First-Pass Elimination of Adinazolam Mesylate in Healthy Male Volunteers

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The pharmacokinetics of adinazolam and *N*-desmethyladinazolam (NDMAD) were studied in 14 healthy male volunteers who received 15 mg adinazolam mesylate orally as a solution and 5 mg adinazolam mesylate intravenously in a crossover design. Two weeks prior to the crossover study, each subject received 5 mg/kg indocyanine green (ICG) as an intravenous bolus injection to estimate liver blood flow. The absolute bioavailability (F), calculated as the dose-corrected ratio of oral to iv adinazolam area under the curve (AUC) values, was found to be 39%. NDMAD AUC values were similar following oral and iv administration, and adinazolam mean absorption time was approximately 0.77 hr. Thus, adinazolam is completely and rapidly absorbed after oral administration in man; the incomplete bioavailability is due to first-pass metabolism. Mean liver blood flow, adinazolam systemic clearance, blood/plasma ratio, and extraction ratio were 1189 ml/min, 498 ml/min, 0.70, and 0.57, respectively. The extraction ratio agrees with that calculated as 1-F (0.62), suggesting that the liver is primarily responsible for first-pass metabolism of adinazolam. The unbound fraction of adinazolam in plasma was 0.31 (range, 0.25–0.36); adinazolam free intrinsic clearance (a reflection of metabolic capacity) was 4285 ml/min (range, 2168–6312 ml/min). These results suggest that the majority of the variability in adinazolam plasma concentrations following oral administration is due to the variability in the metabolic capacity of the liver for adinazolam, rather than variability in plasma protein binding.

KEY WORDS: adinazolam; *N*-desmethyladinazolam; unbound fraction; hepatic extraction ratio; bioavailability.

INTRODUCTION

Adinazolam is a triazolobenzodiazepine which has been shown to elicit benzodiazepine-like and antidepressant activity in animal models (1,2) and has been studied clinically in the treatment of depression (3,4) and panic disorder (5). Adinazolam is characterized by a short plasma half-life (≈2 hr), linear pharmacokinetics at doses of up to 60 mg administered orally, and extensive metabolism to *N*-desmethyladinazolam (NDMAD) (6–8), which is a more potent benzodiazepine receptor agonist than is adinazolam (2,9). More than 95% of an oral dose of adinazolam is converted to NDMAD (10). Adinazolam appears to undergo extensive first-pass conversion to NDMAD after oral dosing; plasma NDMAD peaks rapidly and exceeds adinazolam, with the mean molar ratio of NDMAD-to-adinazolam area under the curve values ranging from 4 to 5.8 (8,11). However, the extent and variability of this first-pass effect have not been determined.

The objectives of this study were (i) to assess the absolute oral bioavailability of adinazolam in healthy male volunteers and (ii) to model the hepatic clearance of adinazolam and determine its intrinsic clearance, using data on plasma protein binding and blood-to-plasma ratio (B/P) of adinazolam and hepatic blood flow, as estimated by indocyanine green (ICG) clearance. This information will be useful in assessing the extent to which various factors account for the variability in plasma concentrations of adinazolam following oral dosing. Since adinazolam and NDMAD are both pharmacologically active, alterations in first-pass metabolism may affect the therapeutic and side-effect profile of adinazolam.

MATERIALS AND METHODS

Subjects

This study was conducted at Harris Laboratories, Inc., Lincoln, NE, following approval by the local Institutional Review Board. Fourteen healthy male volunteers (11 nonsmokers, 3 smokers) were enrolled after providing written informed consent. The age range of the subjects was 20–48 years. Subject weights were within 10% of their ideal body weight (Metropolitan Height and Weight tables) and ranged from 67.1 to 94.3 kg. Subjects were determined to be in good health by physical examination and standard clinical laboratory test and received no known enzyme inducing agents for 30 days prior to the study and no medications during the 7

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days prior to study commencement. During the course of the study, no medications other than those specified in the protocol were taken. Alcohol intake was prohibited for 2 days prior to and on study days.

Study Design

In the first study phase, indocyanine green (ICG) (Cardio-Green, Hynson, Westcott, and Dunning, Cockeysville, MD), 5 mg/kg, was administered by intravenous bolus injection after an overnight fast. The powder was diluted according to the manufacturer's instructions. Blood samples were obtained at 0, 5, 10, 15, 20, 30, 45, and 60 min after dosing. During the sampling period, subjects remained in a supine position. Serum was harvested and frozen until ICG was determined by a specific HPLC technique (12).

Two weeks after ICG administration, subjects received adinazolam mesylate sterile solution as a 15 mg oral dose and a 5-mg infusion according to a randomized two-way crossover design. One week separated each adinazolam treatment. Study medication was administered at 8 AM on day 1 of each phase. Subjects were required to fast from 8 PM the night before dosing until 4 hr after drug administration. Adinazolam mesylate sterile solution (15 ml) was administered orally with 180 ml water; for iv administration, the solution was diluted to a concentration of 0.25 mg/ml with normal saline and administered over 10 min. Subjects remained supine during the first 4 hr after dosing. Venous blood samples (7 ml) were collected into heparinized vacutainers immediately prior to drug dosing and at 0.167, 0.20, 0.25, 0.33, 0.50, 0.75, 1.0, 1.5, 2.0, 3, 4, 6, 8, 12, 16, 20, and 24 hr after the dose. For the iv dose, these times refer to the time after the start of the infusion. Plasma was harvested after centrifugation and frozen until analyzed. Urine samples were collected over the intervals −8–0, 0–2, 2–4, 4–8, 8–12, 12–16, 16–24, and 24–36 hr after dosing. The total volume of urine collected over each interval was measured, and a 20-ml aliquot was frozen for later analysis. At 45 min after dosing, a 20-ml blood sample was collected in a nonheparinized syringe; the blood was allowed to clot, and serum was collected and frozen for subsequent protein binding analysis.

Adinazolam and NDMAD Determination

Adinazolam and NDMAD in plasma were determined by a specific HPLC technique (11). The lower limits of quantitation for adinazolam and NDMAD were 2 and 10 ng/ml, respectively. Standard curves were linear from 2 to 20 and 20 to 200 ng/ml for adinazolam and from 10 to 100 and 100 to 1000 ng/ml for NDMAD. Coefficients of variation were less than 7.4 and 7.1% for adinazolam and NDMAD, respectively. NDMAD in urine was determined by a similar technique (11). Standard curves were linear from 5 to 100 and 100 to 400 ng/ml; the limit of quantitation was 5 ng/ml. The coefficient of variation was less than 5.9%. If concentrations in the samples exceeded those of the standard curve, they were diluted and reassayed.

Protein Binding Determination

Protein binding was determined by equilibrium dialysis. Sufficient ^{14}C-adinazolam (Chemsyn Science Laboratories, Lenexa, KS) was added to serum to achieve a concentration of 50 ng/ml of labeled compound. The buffer used for dialysis was a pH 7.2, 0.133 *M* phosphate buffer; the dialysis time was 8 hr at 37°C. The free fraction of adinazolam in serum (f_p) was calculated as the ratio of buffer-to-serum dpm values.

Blood-to-Plasma (B/P) Determination

A separate blood sample was also collected at 45 min into a heparinized vacutainer tube. The sample was well agitated, and an aliquot of whole blood was frozen for subsequent analysis of adinazolam and NDMAD. Blood concentrations of these compounds were determined by a modification of the HPLC method for plasma. The blood-to-plasma ratio (B/P) was calculated as the ratio of whole-blood concentration to plasma concentration of each compound at 45 min after dosing.

Data Analysis

Pharmacokinetic parameters were determined by noncompartmental techniques (13). The terminal elimination rate constant (β) was determined by linear regression of the terminal portion (final three to six data points) of the logarithmic concentration–time profile. The terminal half-life ($t_{1/2}$) was calculated as

$$t_{1/2} = 0.693/\beta \quad (1)$$

Area under the plasma concentration–time curve (AUC) was determined by trapezoidal rule up to the last time at which a measurable concentration was observed and extrapolated to infinity (14). Area under the first moment curve (AUMC) was determined in an analogous manner. Systemic clearance (Cl) was calculated as

$$Cl = Dose_{IV}/AUC_{IV} \quad (2)$$

Oral clearance (Cl_O) was calculated as

$$Cl_0 = Dose_{PO}/AUC_{PO} \quad (3)$$

Systemic mean residence time (MRT) following the iv dose was described by

$$MRT = AUMC/AUC - T/2 \quad (4)$$

where T is the infusion time. Volume of distribution following the iv dose was calculated by the area method ($V_{d_{area}}$) and moment analysis ($V_{d_{ss}}$) as

$$V_{d_{area}} = Cl/\beta \quad (5)$$

$$V_{d_{ss}} = Cl \cdot MRT \quad (6)$$

Absolute bioavailability (F) of adinazolam following oral administration was calculated as

$$F = \frac{AUC_{PO}\, D_{IV}}{AUC_{IV}\, D_{PO}} \quad (7)$$

Mean absorption time (MAT) was described as

$$MAT = AUMC_{PO}/AUC_{PO} - MRT \quad (8)$$

The absorption rate constant (K_a) could then be calculated as 1/MAT. K_a was also determined by first fitting a biexponen-

tial equation to the postinfusion iv data using the nonlinear least-squares estimation program NONLIN (15) and using the resultant parameters to calculate K_a using the exact Loo–Riegelman method (16). Maximal plasma concentrations (C_{max}) and the times at which they occurred (T_{max}) were determined graphically from the concentration–time profile. NDMAD renal clearance (Cl_{RM}) was calculated as AE/AUC, where AE is the total amount of NDMAD excreted unchanged. The molar ratio of NDMAD-to-adinazolam AUC values (NDMAD/AD) was calculated as

$$\frac{\text{NDMAD}}{\text{AD}} = \frac{\text{AUC}_{\text{NDMAD}} \cdot 351.87}{\text{AUC}_{\text{AD}} \cdot 337.87} \quad (9)$$

Hepatic blood flow (Q) was calculated as (17)

$$Q = Cl_{ICG}/(1\text{-HCT}) \quad (10)$$

where Cl_{ICG} is the systemic clearance of ICG and HCT is the hematocrit. Blood clearance of adinazolam was described as

$$Cl_B = Cl/(B/P) \quad (11)$$

Hepatic extraction ratio (E) of adinazolam was derived using

$$E = Cl/Q \quad (12)$$

Analysis of variance (ANOVA) was utilized to assess differences in selected adinazolam and NDMAD pharmacokinetic parameters between oral and intravenous administration. Model parameters were group, subject nested within group, treatment, and period. Statistical significance was assumed at $P < 0.05$. All parameters except NDMAD/AD met assumptions for normality and homogeneity of variance for ANOVA to be valid (18); NDMAD/AD data were analyzed by ANOVA of the ranked data.

RESULTS

Mean adinazolam and NDMAD concentration–time profiles following iv and po administration are depicted in Figs. 1 and 2. Adinazolam levels following a 15-mg po dose approximated those following the 5-mg iv dose. Postinfusion adinazolam data for the iv dose were best described by a biexponential model, based on the Akaike information criterion (19) and examination of residuals. NDMAD exhibited a rapid and high C_{max} following oral dosing while the NDMAD curve was substantially lower after iv administration of adinazolam.

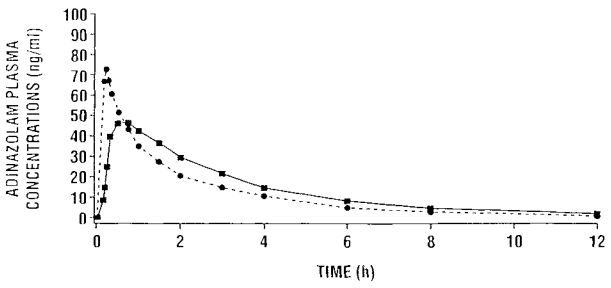

Fig. 1. Mean plasma adinazolam concentration–time profiles following the administration of 15 mg adinazolam mesylate as an oral solution (■) and 5 mg adinazolam mesylate as a 10-min iv infusion (●) in 14 healthy volunteers.

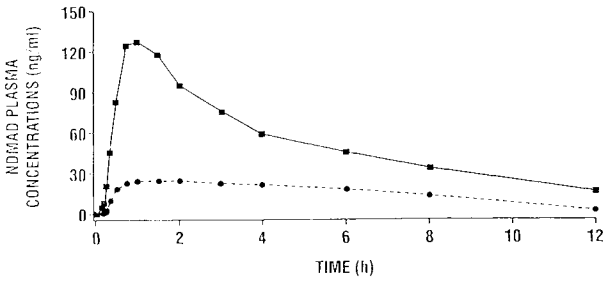

Fig. 2. Mean plasma NDMAD concentration–time profiles following the administration of 15 mg adinazolam mesylate as an oral solution (■) and 5 mg adinazolam mesylate as a 10-min iv infusion in 14 healthy volunteers (●).

Pharmacokinetic parameters of adinazolam are depicted in Table I. Systemic clearance of adinazolam was approximately 498 ml/min; $V_{d_{ss}}$ was approximately 78.8 liter. The mean absorption time of adinazolam was approximately 0.77 hr, with K_a estimated to be 1.93 ± 1.04 hr^{-1}. The mean K_a determined by the Loo–Riegelman method was 2.42 ± 0.41 hr^{-1}. No significant difference was observed in adinazolam half-life between po and iv administration.

NDMAD pharmacokinetic parameters are depicted in Table II. The AUC of NDMAD following po adinazolam administration was approximately 18% lower than that observed after iv administration (on a dose-corrected basis); this difference was statistically significant ($P = 0.022$). Although dose-corrected NDMAD AUC values were similar, dose-corrected C_{max} of NDMAD was approximately 50% lower following iv administration as compared to oral ad-

Table I. Mean (±SD) Pharmacokinetic Parameters for Adinazolam in Plasma Following Administration of 15-mg Oral and 5-mg iv Solutions of Adinazolam Mesylate in 14 Healthy Male Volunteers

	po, 15 mg	iv, 5 mg
AUC (ng/hr/ml)	166	139
	(69.5)	(36.0)
Dose-corrected[a] AUC (ng/hr/ml)	166	417
	(69.5)	(108)
F	0.39	
	(0.08)	
Cl (ml/min)[b]	1330	498
	(405)	(113)
K (hr^{-1})	0.33	0.34
	(0.09)	(0.07)
$t_{1/2}$ (hr)	2.29	2.12
	(0.68)	(0.47)
$V_{d_{area}}$ (L)		88.5
		(16.3)
$V_{d_{ss}}$ (L)		78.8
		(13.4)
MRT (hr)		2.62
		(0.52)
MAT (hr)	0.77	
	(0.68)	

[a] Normalized to a 15-mg dose.

[b] Systemic clearance (Cl) for iv; oral clearance (Cl_0) for oral administration.

Table II. Mean (±SD) Pharmacokinetic Parameters for NDMAD in Plasma Following Administration of 15-mg Oral and 5-mg iv Solutions of Adinazolam Mesylate in 14 Healthy Male Volunteers

	po, 15 mg	iv, 5 mg
AUC (ng hr/ml)	708	285
	(168)	(59.5)
Dose-corrected AUC (ng hr/ml)	708	854
	(168)	(179)
Dose-corrected[a] C_{max} (ng/ml)	141	76.7
	(20.1)	(10.9)
K (hr^{-1})	0.18	0.11
	(0.02)	(0.03)
$t_{1/2}$ (hr)	4.02	6.78
	(0.55)	(1.76)
T_{max} (hr)	1.00	1.68
	(0.35)	(0.37)
NDMAD/AD	4.72	2.18
	(0.91)	(0.34)
Amount of NDMAD excreted in urine (% of dose)	59.1	57.7
	(8.93)	(14.2)
Cl_{RM} (L/hr)	9.74	7.97
	(1.95)	(2.54)

[a] Corrected to a 15-mg dose.

Table III. Individual Data for Adinazolam Extraction Ratio (E), Plasma Free Fraction (f_p), and Liver Blood Flow (Q)

Subject No.	E^a	E^b	f_p	Q (ml/min)
1	0.47	0.66	0.29	1524
2	0.55	0.70	0.32	1756
3	0.79	0.71	0.31	750
4	0.79	0.57	0.34	821
5	0.60	0.56	0.31	1142
6	0.50	0.71	0.36	1222
7	0.53	0.64	0.32	943
8	0.46	0.68	0.33	1689
9	0.57	0.53	0.30	1013
10	0.59	0.62	0.30	1145
11	0.39	0.47	0.25	1194
12	0.56	0.62	0.30	1588
13	1.00	0.58	0.30	1189
14	1.13	0.49	0.28	672
Mean (all subjects)	0.64	0.61	0.31	1189
(SD)	(0.22)	(0.08)	(0.03)	(344)
Mean (subjects 1–12)	0.57	0.62		
(SD)	(0.12)	(0.08)		

[a] Calculated as $E = Cl/Q$, where Cl is systemic clearance.
[b] Calculated as $E = 1 - F$, where F is the absolute bioavailability after oral administration.

ministration. β was significantly larger following po administration ($P = 0.0001$); the NDMAD/AD ratio was significantly larger following oral administration as compared to iv (4.72 vs 2.18, respectively; $P = 0.0001$). The urinary clearance parameters for NDMAD are also summarized in Table II. Cumulative excretion of NDMAD reached plateau values within 24 hr after dosing. The renal clearance and amount of NDMAD excreted in the urine were similar for both oral and iv administration.

Adinazolam free fraction, extraction ratio, and blood flow data are summarized in Table III. The absolute bioavailability of adinazolam was approximately 0.39 and ranged from 0.29 to 0.54. Adinazolam free fraction was 0.31, with a range of 0.25–0.36. The mean B/P ratio was 0.7, with a range of 0.60–0.84. Values for hepatic blood flow ranged from 672 to 1756 ml/min. The mean hepatic extraction ratio was 0.57.

DISCUSSION

Adinazolam is a triazolobenzodiazepine which has pharmacological properties similar to those of alprazolam and triazolam but also exhibits antidepressant activity (1,2). Pharmacodynamic assessments were not performed as part of this study, as the doses administered do no produce overt pharmacological effects (7,10). Adinazolam oral clearance and V_d/F have been previously assessed; iv administration is necessary to determine systemic clearance and V_d. The results of iv administration show that adinazolam V_d is similar to that of alprazolam (20) and triazolam (21); systemic clearance is approximately 10 times greater for adinazolam as compared to alprazolam but is approximately equal to that of triazolam.

Intravenous adinazolam administration allows more definitive description of adinazolam's behavior following oral dosing. Analysis of absorption plots obtained using the Loo–Riegelman approach indicated that absorption occurred by a first-order process. MAT for adinazolam was approximately 0.77 hr, indicating rapid absorption from the GI tract. K_a values obtained by moment analysis and the Loo–Riegelman method were similar and also support this conclusion. β was not different between oral and iv administration, thus adinazolam does not exhibit the flip-flop phenomenon (13). Data for NDMAD pharmacokinetics may also be used to assess the completeness of adinazolam absorption. According to Houston (22,23), the AUC for a primary metabolite is independent of the route of administration, provided that absorption from the extravascular route is complete and little of the parent drug is eliminated renally. Both assumptions are satisfied for adinazolam. Therefore, an estimate of the fraction (f_a) absorbed may be obtained by

$$f_a = \frac{AUC_{PO}(m)}{AUC_{IV}(m)} \tag{13}$$

where AUC(m) refers to the AUC of the metabolite after administration of parent compound by the particular route of administration. Utilizing mean data for dose-corrected NDMAD AUC after oral and iv administration, f_a is estimated to be 0.82. However, this estimate may be biased by the fact that NDMAD β values differed between iv and oral dosing. The iv dosing resulted in lower NDMAD concentrations than oral administration; thus, assay sensitivity was more quickly reached after iv dosing, resulting in less accurate estimates of NDMAD β, AUC, and $t_{1/2}$. A better estimate of f_a may be obtained by examining the urinary excretion of NDMAD after oral and iv administration. The rate of urinary excretion of a metabolite [$dA_e(m)/dt$] may be described by (22)

$$\frac{dA_e(m)}{dt} = f_e(m)\ \mathrm{Cl}(m)\ \mathrm{C}(m) \quad (14)$$

where $f_e(m)$ is the fraction of the metabolite formed from the parent compound which is eliminated without further metabolism, and Cl(m) is the systemic clearance of the metabolite. This may be integrated over time zero to infinity to

$$A_e(m) = f_e(m)\ \mathrm{Cl}(m)\ \mathrm{AUC}(m) \quad (15)$$

where $A_e(m)$ is the total amount of metabolite excreted in the urine after the dose of the parent compound. The ratio of $A_e(m)$ values after oral and iv administration, after cancellation of constant terms [$f_e(m)$, Cl(m)], may be written as

$$\frac{A_{e_{PO}}(m)}{A_{e_{IV}}(m)} = \frac{\mathrm{AUC_{PO}}(m)}{\mathrm{AUC_{IV}}(m)} = f_a \quad (16)$$

Utilizing this equation and dose-corrected values for $A_e(m)$, f_a is calculated to be 1.03. Thus, adinazolam absorption is essentially complete following oral administration.

Adinazolam absolute bioavailability was approximately 0.4, with a range of approximately twofold. This contrasts with alprazolam, which is almost completely bioavailable following oral administration (16), and triazolam, which is approximately 75% bioavailable (17). Based on the similarity of plasma levels and urinary recovery following oral and iv administration of adinazolam, the reason for the low bioavailability of adinazolam appears to be presystemic conversion to NDMAD.

Liver blood flow was measured in order to allow the calculation of the hepatic extraction ratio of adinazolam in these subjects. The B/P ratio was also measured to allow conversion of plasma clearance to blood clearance in the calculation of E by Eq. (12). An *ex vivo* method for determining B/P was used, since this has been shown to be superior to *in vitro* methods for diazepam (24). In two subjects, the calculated E value was >1; these data suggested extremely low bioavailability of adinazolam in these subjects, which was not observed (Table III). Liver blood flow has been shown to be quite variable and may be influenced by posture, exercise, etc. (25). These aberrant values for E in these two subjects were probably due to variability in the measured liver blood flow over the study period; data from these two subjects were excluded from further analysis. The mean values for adinazolam extraction ratio was 0.57, which approximates the value of 0.62 (for 12 subjects) obtained by

$$E = 1 - F \quad (17)$$

where F is the absolute bioavailability of adinazolam obtained after oral dosing. The agreement between the extraction ratios obtained by Eqs. (12) and (17) suggests that the liver is the primary organ responsible for the presystemic elimination of adinazolam following an oral dose.

Since complete absorption and exclusive hepatic metabolism seem to describe the disposition of adinazolam in man, the free intrinsic clearance ($\mathrm{Cl_i}$) of adinazolam may be calculated by [assuming a well-stirred model for hepatic elimination processes (26)]

$$\mathrm{Cl_i} = \mathrm{Cl_0}/f_p \quad (18)$$

Mean $\mathrm{Cl_i}$ was 4285 ml/min, with a range of 2168–6312 ml/min. The oral clearance of adinazolam varied over a fourfold range, from 535 to 2000 ml/min. Adinazolam f_p was much less variable, with a range of 0.247–0.355. Thus, the majority of the variability in adinazolam plasma concentrations (and hence $\mathrm{Cl_0}$) following oral dosing is due to intersubject variability in the metabolic capacity for adinazolam, rather than to variability in adinazolam free fraction.

Tobacco smoking affects the pharmacokinetics of several drugs, because of its effects on oxidative metabolism (27–29). Since only three smokers (>10 cigarettes/day) were included in this trial, formal statistical examination of smokers and nonsmokers would not be appropriate. Examination of the individual subject data revealed no clear trends toward kinetic differences between smokers and nonsmokers. Further study, using an appropriate design, would be necessary to address differences in adinazolam pharmacokinetics between smokers and nonsmokers.

In conclusion, adinazolam appears to be absorbed rapidly and completely following oral administration of a solution of its mesylate salt, but the absolute bioavailability of adinazolam is only 40%. The low bioavailability is apparently due solely to presystemic conversion of adinazolam to NDMAD in the liver. The absolute bioavailability varies over a twofold range, due primarily to variability in hepatic intrinsic clearance. The effect of variability in the absolute bioavailability of adinazolam must be weighed in relation to the relative effects of adinazolam and NDMAD on the therapeutic/side effects produced by these compounds.

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