Pharmacokinetics and Pharmacodynamics of Midazolam After Intranasal Administration

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This study aimed to characterize the pharmacokinetics and pharmacodynamics of midazolam after intranasal administration to healthy volunteers. Eight participants were given 0.25 mg/kg intranasally and 2 mg intravenously in a randomized, crossover fashion. Blood samples for determination of plasma concentrations of midazolam and measures of cognitive function (using the digit symbol substitution test) were obtained at baseline and 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes after administration of study medications. Plasma samples were analyzed by gas chromatography (% coefficient of variation <10%). Pharmacokinetic data were fitted using iterative two-stage analysis to a two-compartment model. Pharmacodynamic data were fitted by a baseline subtraction Hill-type model. The mean (SD) for total clearance, distributional clearance, volume of distribution in the central compartment, volume of distribution in the peripheral compartment, absorption rate constant, bioavailability, and half-life were 0.57 (0.26) L/hr/kg, 0.31 (0.29) L/hr/kg, 0.27 (0.14) L/kg, 0.67 (0.11) L/kg, 2.46 (1.72) hr^{-1}, 50% (13%), and 3.1 (0.84) hours, respectively. The mean (SD) for the concentration at which the effect is half maximal (EC_{50}) and the maximal effect or the maximal change in effect measure from baseline (E_{max}) were 63.1 (21.2) ng/mL and 52.8 (21.1) correct substitutions, respectively. After intranasal administration, midazolam concentrations rapidly achieve values considered sufficient to induce conscious sedation and produce predictable changes in digit symbol substitution score.

Clinical efficacy of midazolam for the induction of sedation, reduction of anxiety, and induction of amnesia is well documented after intravenous[1,2] and oral[3] administration. Despite the advantages of rapid sedative effects, there are disadvantages associated with intravenous administration, primarily the necessity of an injection. In patients with a fear of needles and injections, this route of administration may precipitate fear and anxiety. In an attempt to reduce anxiety, while obviating the use of anxiety-potentiating injections, intranasal administration has been used, primarily in pediatric patients, for the induction of conscious sedation. Although a limited amount of intranasal pharmacokinetic data is available in pediatric patients, no information is available regarding the plasma concentration profile and pharmacokinetics of midazolam after intranasal administration of midazolam to adults. The purpose of this study, therefore, was to evaluate the pharmacokinetics and pharmacodynamics of midazolam after intranasal administration to adult volunteers.

METHODS

Study Conduct

The study was approved by the Institutional Review Board of Millard Fillmore Health Systems (Buffalo,

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NY). Before enrollment, all volunteers gave written informed consent.

Healthy male and nonpregnant female nonsmokers were considered eligible for inclusion in the study if they were at least 18 years old. Potential participants were excluded if there existed a history of hepatitis; renal, respiratory, cardiovascular, or psychiatric disease; sensitivity to benzodiazepines or lidocaine; drug or ethanol abuse; or if women were not practicing a medically approved method of contraception.

Eight volunteers (six men, two women) were enrolled in the nonblind, randomized, crossover study. Within 4 days before the first study day, participants were oriented to the tests of cognitive function to be used (i.e., digit symbol cognitive function substitution test [DSST]). Administration of practice tests was repeated until stable baseline test scores were achieved. Volunteers were assigned randomly to groups regarding the order of administration of the intranasal and intravenous doses of midazolam.

Volunteers reported to the study unit at 7:00 AM each study day after an 8-hour overnight fast. They were continued to fast until 2 hours after administration of the study drug, at which time they were provided with a light breakfast (juice and muffin). Caffeine-containing foods and beverages were avoided. An intravenous catheter was placed into a peripheral vein in the nondominant arm. Baseline blood samples were obtained, and the DSST was administered. Doses of study medication were then administered.

Doses administered as intravenous injections consisted of a single 2-mg dose of midazolam administered as intravenous bolus doses through a heparin lock over 2 minutes. After administration, the heparin lock was flushed with two separate 10-mL saline flushes. After a minimum 4-day washout period, participants were crossed over to the remaining treatment. Vital signs, including heart rate, blood pressure and oxygen saturation, were monitored continuously throughout each study day.

Five minutes before intranasal administration, volunteers were administered two sprays of 4% topical lidocaine into each nostril. Doses of study medication administered intranasally consisted of a single 0.25-mg/kg dose of midazolam. The study medication was drawn up, immediately before administration, into syringe of the appropriate volume from a stock solution consisting of the intravenous 5-mg/mL concentration solution. The needle was removed from the syringe, and an intravenous cannula was attached, allowing a flexible tube to be inserted into the nares for administration. The intranasal dose was administered at a rate of 1 mL/min, with administration alternated between nostrils in 1-mL increments. Volunteers were instructed to inhale with each administration and to refrain from swallowing for as long as comfortably possible.

After administration of study medication (2 hours), blood samples (5 mL) were collected from the intravenous catheter into K_3-EDTA Vacutainer tubes (Becton-Dickinson Vacutainer Systems, Franklin Lakes, NJ) at 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes. Samples were centrifuged immediately for 10 minutes, and plasma was harvested and frozen at −20°C until analyzed for midazolam concentration.

Digit symbol substitution tests were performed at baseline and 10, 30, 60, 90, 120, 180, 240, and 360 minutes after infusion of the study medications. The number of correct substitutions during each 90-second testing interval were counted. Different versions of the DSST were administered at each measurement time.

Assay of Samples

Plasma samples were analyzed for midazolam concentrations using a slightly modified version of the gas chromatography method of De Kroon et al.[4] Standard curves were prepared over the range of 10 ng/mL to 300 ng/mL. Aliquots of patient plasma samples were treated with 250 μL of water and 20 μL of a 500 ng/mL diazepam internal standard solution. Solid-phase extraction was performed using 100-mg C$_{18}$ cartridges. Benzodiazepines were eluted with 500 μL of methanol. After evaporation under N_2 at 50°C, the residue was reconstituted with 50 μL of toluene/methanol/acetone (85/15/5). Aliquots of these reconstituted solutions were injected onto a Varian (Varian Chromatograph Systems, Walnut Creek, CA) 3400 GC using an Alltech (Alltech Associates Inc., Deerfield, IL) 6 meter by 1/8-inch OV17 column with nitrogen as the carrier gas. The sensitivity of the assay with 1 μL of sample was 10 ng/mL,and was linear over the range of 10 ng/mL to 300 ng/mL. Overall, the % coefficients of variation of the assay were 9.9%, 4.5%, and 9.6% at concentrations of 15 ng/mL, 80 ng/mL, and 260 ng/mL, respectively.

Pharmacokinetic/Pharmacodynamic Modeling

Iterative two-stage analysis using the computer software package Adapt[5] (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA) was performed to fit candidate pharmacokinetic and pharmacodynamic models to the plasma concentration–time and pharmacodynamic data. An explanation of this technique is provided elsewhere.[6] Model discrimination was performed by

inspection of residuals and Akaike's information criterion.[7]

Plasma concentration time data after the intranasal and intravenous doses were simultaneously fitted using a linear, two-compartment intravenous injection and nasal absorption model. Modeling incorporated a residual variance model in which the standard deviations of the observations were related linearly to the fitted values. The parameters estimated for midazolam included the volume of distribution in the central compartment (V_c), volume of distribution in the peripheral compartment (V_p), distributional clearance (Cl_d) for both intranasal and intravenous administration and total clearance (Cl), absorption rate constant (K_a), and bioavailability (F) for intranasal administration. Initial modelling allowed V_c, V_p, and Cl_d to differ between intranasal and intravenous administration, with Cl assumed to be similar.

Pharmacokinetic parameter estimates obtained from the initial modeling process were fixed in each volunteer, and pharmacodynamic measures were subsequently modeled. Plasma concentration DSST effect data were fitted by the following baseline subtraction Hill-type equation:

$$E = E_o \frac{E_{max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

where E_o is the baseline effect, E_{max} is the maximal effect or the maximal change in effect measure from baseline, EC_{50} is the concentration at which the effect is ½ maximal, C is the plasma concentration of midazolam, and Γ is the slope term. Despite the assumption that the learning curve was complete before study, it was decided to model the baseline effect. On determining the appropriate pharmacodynamic model, both plasma concentrations and pharmacodynamic measures were simultaneously fitted by the pharmacokinetic and pharmacodynamic models.

RESULTS

Eight healthy volunteers were enrolled in this investigation. Of these, six were men and two were women. The mean (SD) age and weight of participants were 29.5 (5.2) years and 77.9 (16.6) kg, respectively. A summary of the demographic characteristics of participants is provided in Table I. Treatment was well tolerated by all volunteers except subject no. 5. Within 10 minutes of administration of the intranasal dose (on study day 2), this volunteer became lethargic, difficult to arouse, and hypotensive. Flumazenil at 2-mg was administered intravenously with prompt reversal of the lethargy and improvement in blood pressure. Pharmacodynamic data for subject no. 5 was subsequently considered uninterpretable for analysis. As flumazenil has been shown to have no significant effect on midazolam pharmacokinetics,[8] however, the concentration–time data for this volunteer was included in the pharmacokinetic analysis.

TABLE I

Subject Demographic Information

Subject No.	Age (yr)	Weight (kg)	Gender
1	28	82.7	M
2	31	72.7	M
3	30	109	M
4	24	93.2	M
5	26	72.3	M
6	29	72.3	M
7	41	60.0	F
8	27	60.9	F
Mean	29.5	77.9	
SD	5.2	16.6	

M, male; F, female.

Plots of midazolam plasma concentration–time curves for intranasal and intravenous administration are shown in Figures 1 and 2, respectively. Midazolam was absorbed rapidly after intranasal administration, with maximal concentrations achieved with a mean (range) of 25 (10–48) minutes after the initiation of administration. Maximal concentrations were variable with mean (range) values of 147 (91.3–224.3) ng/mL. A two-compartment model was statistically superior for describing the data in all but subject no. 3. The concentration–time profile for subject no. 3 exhibited dual peaks, with the first peak occurring 20 minutes after administration and the second peak occurring 120 minutes after administration (Figure 3). To describe the dual peak phenomenon adequately in this volunteer, modeling incorporated both intranasal and oral absorption components with a lag time to the onset of oral absorption.

The mean (SD) values for Cl, Cl_d, V_c, V_p, K_a, and half-life ($t_{1/2}$) were 0.57 (0.26) L/hr/kg, 0.31 (0.29) L/hr/kg, 0.27 (0.14) L/kg, 0.67 (0.11) L/kg, 2.46 (1.72) hr^{-1}, and 3.1 (0.84) hours, respectively. Mean (SD) values of 50% (13%) of the dose were absorbed after intranasal administration. A summary of parameter values for individual participants is provided in Table II.

Plots of DSST score-versus-time curves for intranasal administration are shown in Figure 4. Impairment of participants' performances was evident early

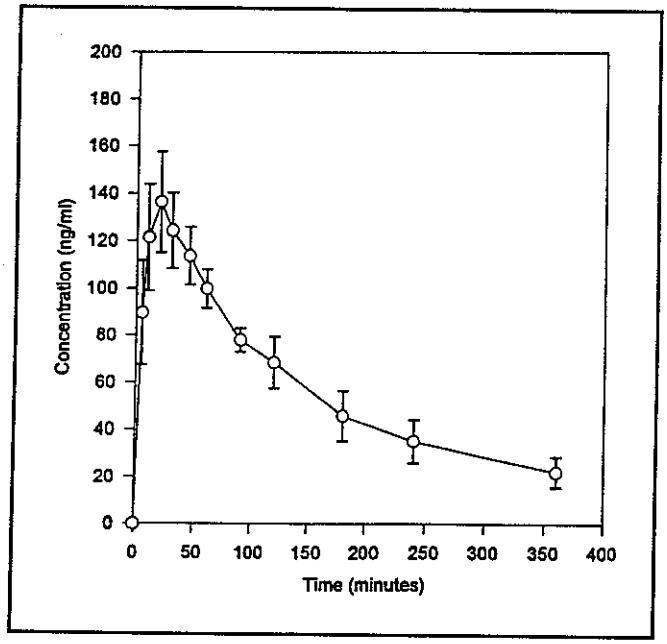


Figure 1. Plasma concentration–time profiles of midazolam after intranasal administration of a 0.25-mg/kg dose. Each point (○) represents the mean value; error bars represent standard errors.

after administration, with maximal impairment occurring 30 minutes (range, 15–120 minutes) after administration of the intranasal dose. The maximal reduction in DSST score was variable, with percent reductions ranging from 33% to 97%.

A representative plot of the midazolam plasma concentration–effect profile for subject no. 4 is shown in Figure 5. No hysteresis loops were identified in any of the volunteers. The mean (SD) values for EC_{50} and E_{max} were 63.1 (21.2) ng/mL and 52 (21.1) correct substitutions, respectively. A summary of individual values is provided in Table III.

DISCUSSION

The intranasal route of administration for midazolam may represent an attractive alternative to the conventional intravenous and oral routes of administration for inducing conscious sedation. A large group of patients, including those with mental disabilities and violent and combative patients, often pose difficulties when medications are administered to induce sedation before procedures such as dental work. In these patients, the anxiety associated with the procedure is often exacerbated by the fear and anticipated pain of receiving an injection. At the authors' institution, these patients often require general anesthesia and the use of an operating room suite to sedate them.

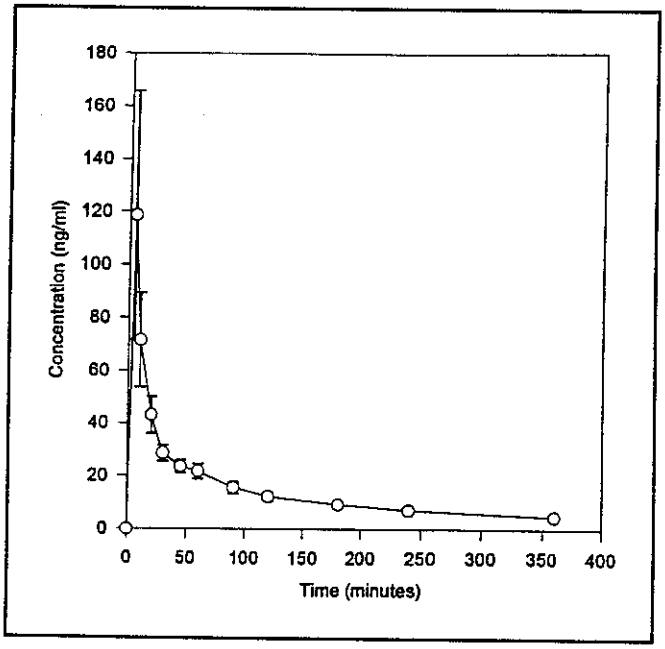


Figure 2. Plasma concentration–time profile of midazolam after intravenous administration of a 2-mg fixed dose. Each point (○) represents the mean value; error bars represent standard errors.

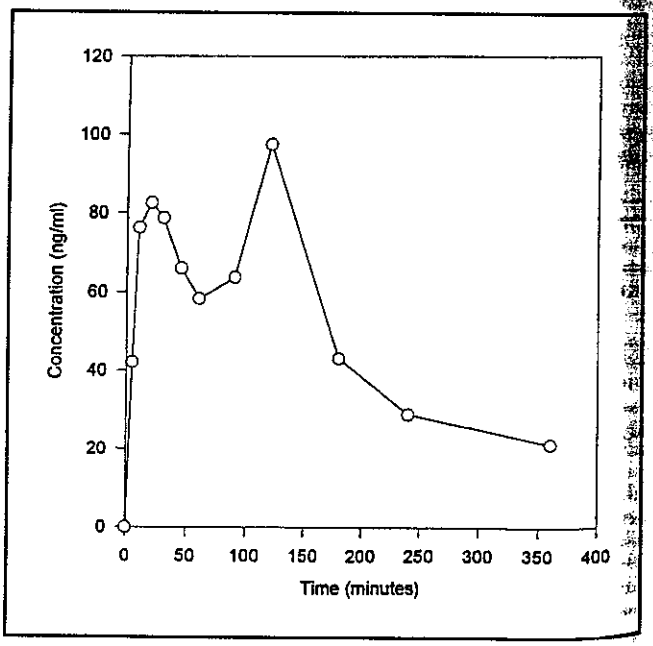


Figure 3. Plasma concentration–time profile of midazolam after intranasal administration in subject no. 3.

TABLE II

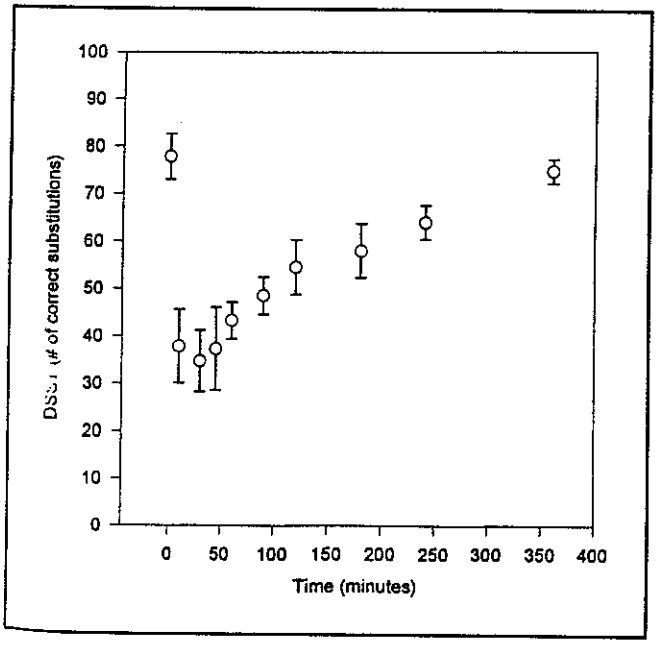
Summary of Pharmacokinetic Parameters of Midazolam after Intranasal Administration

Subject No.	Vc (L/kg)	Vp (L/kg)	Cld (L/hr/kg)	Clt (L/hr/kg)	$t_{1/2}$ (hr)	Ka (hr^{-1})	F
1	0.021	0.66	0.39	0.26	3.0	1.5	0.53
2	0.39	0.65	0.38	0.45	2.5	1.4	0.46
3	0.25	0.81	0.43	0.31	3.4	1.8	0.49
4	0.19	0.73	0.71	0.17	4.4	4.3	0.41
5	0.27	0.79	0.97	0.19	4.2	1.4	0.76
6	0.20	0.47	0.91	0.23	2.3	4.8	0.44
7	0.34	0.57	0.42	0.35	2.5	2.7	0.33
	0.46	0.67	0.33	0.55	2.5	1.7	0.56
Mean	0.27	0.67	0.57	0.31	3.1	2.5	0.50
SD	0.14	0.11	0.26	0.29	0.84	1.7	0.13

Vc, volume of distribution in central compartment; Vp, volume of distribution in peripheral compartment; Cld, distributional clearance; Clt, total clearance; $t_{1/2}$, half-life; Ka, absorption rate constant; F, bioavailability.

successfully to allow performance of the dental procedures. Clearly, any alternative that induces sedation effectively while avoiding the use of general anesthesia and operating room time has significant implications not only for patient safety but also for the cost of routine dental surgical procedures.

To the authors' knowledge, this study is the first to model the disposition of midazolam after intranasal administration to adults. Previously, Walbergh et al[13] studied the concentration–time profile of both intravenous and intranasal midazolam after administration to pediatric patients. However, in this study, only maximal concentrations and the time to attain these concentrations were determined. Their finding of a mean (± SD) peak concentration of 72.2 (± 27.3) ng/mL and time to peak concentration of 10.2 (± 2) minutes suggests that rapid attainment of significant



re 4. Digit symbol substitution test (DSST) score during each econd testing session. Each point (○) represents the mean value; error bars represent standard errors.

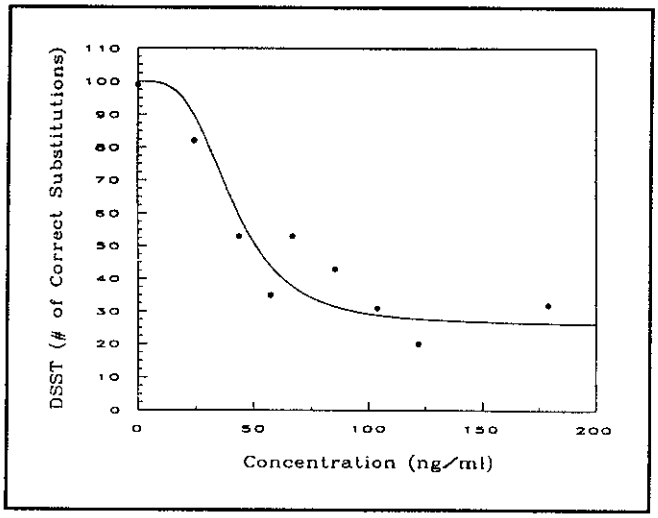


Figure 5. Representative true (●) and predicted (solid line) digit symbol substitution test (DSST) score versus the plasma concentration curve for midazolam for subject no. 4.The DSST score is the number of correct substitutions completed during the 90-second testing session.

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