

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 (EC₅₀) 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 oral³ administration. Despite the advantages of rapid sedative effects, there are disadvantages associated with intravenous administration, primarily the ne-

cessity 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 ad-

ministration and to refrain from swallowing for as long as comfortably possible.

After administration of study medication (hours), blood samples (5 mL) were collected from the intravenous catheter into K₃-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 μ L of water and 20 μ L of a 500 ng/mL diazepam internal standard solution. Solid-phase extraction was performed using 100-mg C₁₈ cartridges. Benzodiazepines were eluted with 500 μ L of methanol. After evaporation under N₂ at 50°C, the residue was reconstituted with 50 μ L 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 μ L 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 Adapt⁵ (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

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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:

$$E = E_0 \frac{E_{\max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

where E_0 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 $1/2$ 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

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.

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.

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

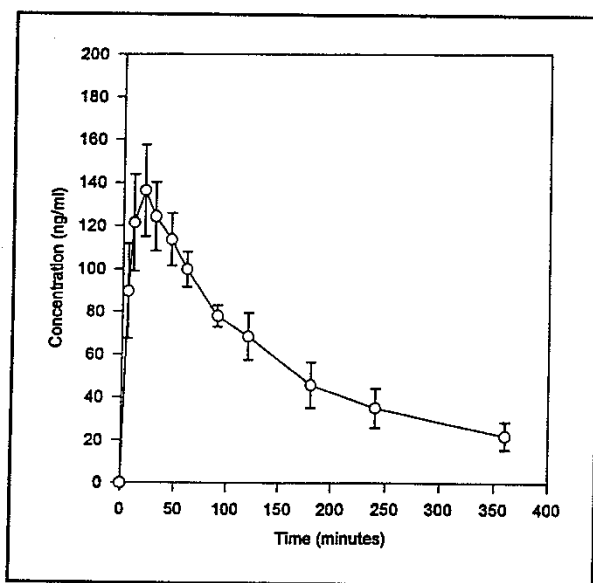


Figure 1. Plasma concentration-time profiles of midazolam after intranasal administration of a 0.25-mg/kg dose. Each point (O) represents the mean value; error bars represent standard errors.

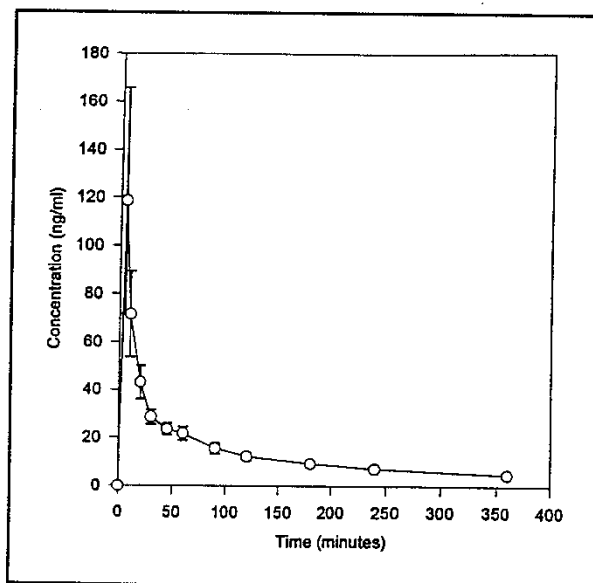


Figure 2. Plasma concentration-time profile of midazolam after intravenous administration of a 2-mg fixed dose. Each point (O) represents the mean value; error bars represent standard errors.

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 percentage 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.

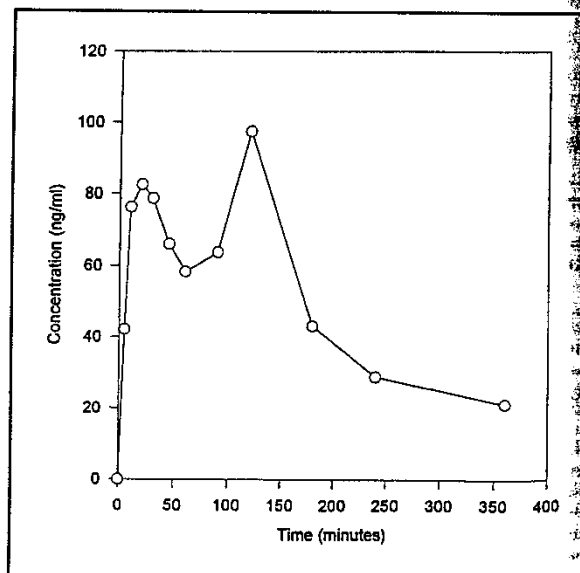


Figure 3. Plasma concentration-time profile of midazolam after intranasal administration in subject no. 3.

TABLE II

Summary of Pharmacokinetic Parameters of Midazolam after Intranasal Administration

Subject No.	Vc (L/kg)	Vp (L/kg)	Cld (L/hr/kg)	Cl _t (L/hr/kg)	t _{1/2} (hr)	K _a (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; Cl_t, total clearance; t_{1/2}, half-life; K_a, absorption rate constant; F, bioavailability.

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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 al¹³ 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 ($\pm$ SD) peak concentration of 72.2 ($\pm$ 27.3) ng/mL and time to peak concentration of 10.2 ($\pm$ 2) minutes suggests that rapid attainment of significant

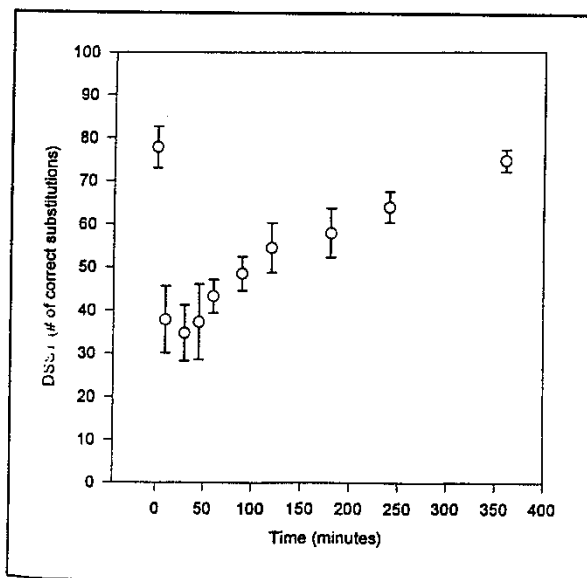


Figure 4. Digit symbol substitution test (DSST) score during each second testing session. Each point (○) represents the mean value; error bars represent standard errors.

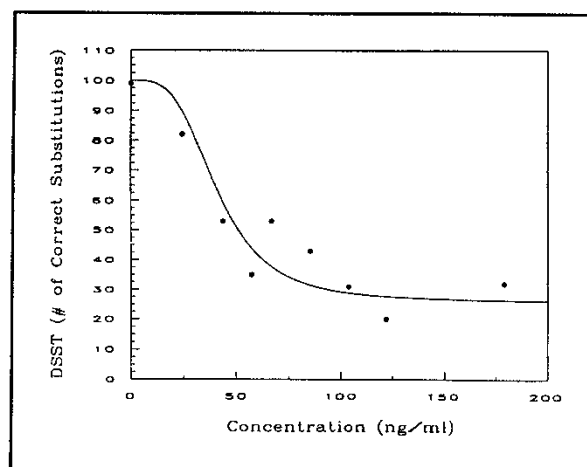


Figure 5. Representative true (●) and predicted (solid line) digit symbol substitution test (DSST) score versus the plasma concentration curve for midazolam for subject no. 4. The DSST score is the number of correct substitutions completed during the 90-second testing session.

TABLE III

Summary of Pharmacodynamic Parameters of Midazolam after Intranasal Administration

Subject No.	E ₀ (baseline no.)*	E _{max} (change from baseline)†	EC ₅₀ (ng/mL)	G
1	69.3	44.4	75.5	2.54
2	66.0	33.9	62.3	2.74
3	83.5	29.7	29.5	4.15
4	100.0	72.7	41.3	3.48
5	NA‡	NA‡	NA‡	NA‡
6	73.6	79.5	86.1	2.40
7	74.4	72.0	83.3	0.90
8	84.0	37.3	63.8	3.89
Mean	78.7	52.8	63.1	2.87
SD	11.5	21.1	21.2	1.10

* Baseline number of correct substitutions.

† Change from baseline in the number of correct substitutions.

‡ Pharmacodynamic data unavailable due to flumazenil administration.

E₀, baseline effect; E_{max}, maximum effect or maximum change in effect; EC₅₀, concentration at which effect is 1/2 maximal; NA, not available.

plasma concentrations may be obtained after intranasal administration of 0.1 mg/kg. Similarly, Rey et al¹⁴ conducted a comparative pharmacokinetic study of intravenous and intranasal midazolam administration to pediatric patients. Mean time to achieve a mean ($\pm$ SD) maximal concentration of 104 ($\pm$ 32) μ g/L was 12 ($\pm$ 4) minutes after a dose of 0.2 mg/kg. Additionally, the investigators found higher apparent plasma clearances and volumes of distribution after intranasal administration.

Maximal concentrations in the present investigation were attained a mean (range) of 25 (10–48) minutes after the intranasal administration of midazolam. Although this time is longer than those previously reported in pediatric patients,^{13,14} the results are of limited clinical significance. It has been reported previously that the threshold concentration for induction of conscious sedation is 40 ng/mL.^{15–17} Evaluation of the mean intranasal plasma concentration–time profile shows that participants attained concentrations exceeding this threshold concentration as early as 10 minutes after administration. Mean plasma concentration was sustained above this threshold concentration for 90 to 180 minutes (range, 90–360 minutes in individual volunteers). Although maximal effects would not be expected until 25 minutes after administration, adequate conscious sedation of sufficient duration for performance of short procedures would be anticipated.

The rapid absorption of intranasal midazolam in

the present study is consistent with observations after oral¹⁵ and intramuscular¹⁸ administration. Bioavailability in the present study ($50 \pm 13\%$) is similar to values obtained after oral administration (42–17%).¹⁵ Intranasal administration of medications additionally has been thought to be associated with several advantages over oral administration, including avoidance of hepatic first-pass metabolism, intestinal wall metabolism, and destruction of medications in gastrointestinal fluids.¹⁹ However, the nasal mucosa may serve as a barrier to the entry of medication into the systemic circulation. Cytochrome P-450 enzymes, at concentrations 5% of those found in the liver, have been identified within the human nasal mucosa.²⁰ A potential explanation for the less than complete bioavailability after intranasal administration may be potential metabolism of midazolam by cytochrome P-450 on its passage across the nasal mucosa.

Intranasal administration of midazolam for induction of conscious sedation has been used successfully in adult patients for phlebotomy in an agitated and frightened patient,⁹ for management of claustrophobia during magnetic resonance imaging,¹⁰ and for dental surgery.^{11,12} Doses administered in these reports have varied from a weight-based dose ranging from 0.2 mg/kg to 0.25 mg/kg^{9,11,12} to a fixed-dose administration of 0.5 mg repeated once if ineffective. In the present study, doses of 0.25 mg/kg were used, resulting in a relatively large volume of solution being instilled into the nares (4–5 mL). Despite the maximal volume of the nares of approximately 20 mL,²¹ the larger administered volume made swallowing of solution more likely. Despite the use of what was believed to be a sufficiently slow administration rate in this study, it was likely that some of the participants swallowed medication. The delayed time to reach maximum concentration (t_{max}) is consistent with values reported after oral administration¹⁵ and may represent not only nasal absorption but also concomitant gastrointestinal absorption. The plasma concentration–time profile after intranasal administration in subject no. 3 supports this notion. The dual peaks occurring at 20 and 120 minutes after administration are consistent with anticipated maximal concentrations resulting from nasal absorption followed by oral absorption. During administration of the intranasal study dose, this participant indicated that he believed he was swallowing medication. The second peak, occurring at 120 minutes, coincides with the ingestion of the 2-hour light breakfast given after administration. Associated with this second peak was impairment of the participant's cognitive performance as measured by DSST score. The commercially available preparation of midazo-

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lam exists in a hydrophilic form at the formulated pH of 2. After oral ingestion, midazolam was maintained in a low pH environment, thereby preventing the conversion of midazolam to the ring open, lipophilic form. The ingestion of food, with its buffering of the gastric acidity and subsequent conversion of midazolam to its lipophilic structure, may have facilitated the absorption of the orally administered fraction of the intranasal dose.

Previous experience of the authors' group in dental patients and that reported in a letter by Lugo et al²² indicate that the administration of the undiluted injectable formulation of midazolam is associated with irritation, burning, irritation, and general discomfort for patients. The discomfort evident in the authors' previous experiences was such that patients who previously had desired an alternative to injections later indicated they would prefer the injection over intranasal drops. Lidocaine was therefore administered as a topical nasal spray before administration of the intranasal dose of midazolam to minimize the occurrence of these side effects. Each spray delivered approximately 0.05 mL or 2 mg/spray; therefore, the total dose received by participants was 8 mg. Although it is possible that the administration of topical lidocaine may have induced local changes in the nasal mucosa thereby affecting absorption, the method used represents the anticipated administration technique in clinical practice.

The DSST was used to evaluate the pharmacodynamic response to the intranasal dose of midazolam. This test was chosen based on its simplicity, ease of administration, and documented sensitivity as a measure of benzodiazepine-induced alterations in cognitive performance.²³ The DSST is a measure primarily of cognitive and psychomotor skill; however, both a sedation visual analog scale and an observer's assessment of alertness/sedation scale have been shown to correlate with the DSST test when used after intravenous administration of midazolam.²⁴ Although it was not specifically evaluated in this investigation, it may be hypothesized that changes in DSST score evident after intranasal administration of midazolam would be representative of changes in level of sedation.

No time-dependent relationship between plasma midazolam concentrations and pharmacodynamic response was seen. This finding is in contrast to results of other investigators, who describe hysteresis in both DSST²⁵ and electroencephalogram⁸ pharmacodynamic measures associated with midazolam plasma concentrations after intravenous administration. The apparent delay between plasma concentration and pharmacodynamic effect has a physiologic basis when it is considered that systemically admin-

istered medications must cross the blood-brain barrier to induce impairment of cognitive performance or alterations in electroencephalographic measures. The lack of hysteresis in the present study may be related specifically to the intranasal route of administration. It has been suggested that communications exist between the subarachnoid space and nasal cavities, cranial and nasal cavities, and the perineural sheaths in the olfactory nerve and the nasal mucosa.²⁶ It may be hypothesized that these communications represent a route for the rapid and direct entry of intranasally administered midazolam into the central nervous system. If this hypothesis was valid, one would expect a rapid onset of effect and lack of hysteresis on effect-concentration plots, due to the circumvention of the blood-brain barrier. As pharmacodynamic measures associated with the intravenous dose were not determined in this study, effect-concentration profiles and pharmacodynamic parameter values could not be compared to support or refute this hypothesis.

Problems associated with intranasal administration of midazolam include the preadministration use of intranasal lidocaine and the potential for swallowing. Use of administration methods such as atomizers to reduce the administered particle size or slower administration rates via injection may minimize the swallowing of medication seen with administration at 1 mL/min using a syringe. Despite the disadvantages, this route represents a viable alternative for patients in whom intravenous administration is not feasible. Intranasal administration of midazolam at a dose of 0.25 mg/kg resulted in predictable effects on cognitive performance and concentration profiles anticipated to provide adequate conscious sedation for minor surgical and diagnostic procedures. Further investigations are necessary to evaluate the comparative pharmacodynamics after intranasal and intravenous administration to support or refute the hypothesis regarding direct transport between the nasal mucosa and subarachnoid space.

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