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Bioavailability and Pharmacokinetics of Lorazepam after Intranasal, Intravenous, and Intramuscular Administration

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The purpose of this study was to evaluate the pharmacokinetic profile of intranasal lorazepam in comparison to currently established administration routes. Eleven healthy volunteers completed this randomized crossover study. On three occasions, each separated by a 1-week washout, subjects received a 2 mg dose of lorazepam via the intranasal, intravenous, or intramuscular route. Blood samples were collected serially from 0 to 36 hours. Noncompartmental methods were used to determine pharmacokinetic parameters. Lorazepam was well absorbed following intranasal administration with a mean (%CV) bioavailability of 77.7 (11.1). Intranasal administration resulted in a faster absorption rate than intramuscular administration. Elimination profiles were comparable between all three routes. The concentration-time profile for intranasal delivery demonstrated evidence of a double peak in several subjects, suggesting partial oral absorption. Females were found to have significantly higher AUC values than males for all three delivery routes. Overall, this study demonstrated favorable pharmacokinetics of intranasal lorazepam in relation to standard administration methods. Intranasal delivery could provide an alternative, noninvasive delivery route for lorazepam.

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Lorazepam, a benzodiazepine, is available both orally and parenterally.[1] It is used clinically as an anxiolytic, as a treatment for status epilepticus, preoperatively, and as an adjunct for nausea management, and it has recently been studied for its potential use in acute psychotic situations.[1-5] In many of these cases, it is necessary to administer lorazepam via the intravenous (IV) or intramuscular (IM) route for rapid onset of action and assured dose bioavailability.

An alternative route of administration, one that would avoid the use of needles while continuing to provide rapid effect, should prove extremely useful in a variety of clinical settings. In particular, it would be highly beneficial in the pediatric setting. Alternative routes of delivery include rectal or intranasal (IN) administration. The rectal route has been evaluated for lorazepam but was found to have a slow absorption rate in humans[6] and was found to undergo extensive first-pass metabolism in dogs.[7] The IN route has been studied previously in humans as well.[8] It was found to have a moderate concentration profile, as evidenced by its 51% absolute bioavailability. Other benzodiazepines, such as midazolam[9,10] and diazepam,[8,11] have also been examined intranasally in humans with promising results.

The purpose of this study was to determine whether IN administration would provide comparable bioavailability and pharmacokinetic profiles with respect to intravascular and intramuscular delivery.

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MATERIALS AND METHODS

Subjects

Twelve (6 male, 6 female) healthy volunteers (Table I) within the age range of 18 to 35 years were eligible for enrollment in this study. The screening evaluation con-

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Table I Subject Demographics and Administration Sequence

Subject	Age (years)	Weight (kg)	Gender	Ethnicity	Dosing Sequence		
					Period 1	Period 2	Period 3
1	25	58.6	F	Caucasian	IV	IM	IN
2	20	56.8	F	Caucasian	IN	IV	IM
3	NA[a]	NA[a]	F	Caucasian	IM	NA[a]	NA[a]
4	22	75.2	F	Caucasian	IM	IV	IN
5	20	65.9	F	Caucasian	IV	IN	IM
6	20	67.7	F	Caucasian	IN	IM	IV
7	20	62.7	M	Caucasian	IM	IV	IN
8	21	72.3	M	Caucasian	IN	IM	IV
9	26	79.8	M	Asian	IV	IN	IM
10	21	80.4	M	Caucasian	IM	IN	IV
11	26	77.5	M	Caucasian	IN	IV	IM
12	21	79.5	M	Caucasian	IV	IM	IN

IV, intravenous; IM, intramuscular; IN, intranasal.
a. NA, not applicable. Subject 3 dropped from the study following the first dosing period.

sisted of a medical history, physical and nasal examinations, and clinical laboratory tests. Subjects were excluded from participation based on the presence of any clinically significant laboratory values or disease states, including acute or chronic nasal symptoms and physical abnormalities of the nasal passage. Subjects were also excluded for tobacco use within the past 2 years, presence of alcohol or substance abuse within the past 5 years, and pregnancy or if not willing to abstain or use barrier methods of birth control during the study period. Written informed consent was obtained. The institutional review board of the University of Kentucky approved this study.

Study Procedures

This was a randomized, three-way crossover, single-dose study with each treatment separated by a washout period of 1 week. All 12 subjects reported to the study center at 18:00 the night prior to the study day and remained in the center until the last blood draw was obtained, approximately 36 hours after dosing. During each experiment period, subjects were administered the study drug via either the IV, IM, or IN route as determined by a previously constructed randomization schedule (Table I).

Drug administration occurred at approximately 08:00 on each study day. Except for water ad libitum or a caffeine-free drink or juice, subjects underwent an overnight fast of at least 8 hours. No fluids were allowed 1 hour prior to or after dosing. Standardized meals were provided at 12:00 and 18:00 each day and breakfast at 08:00 on day 2 of each study period. No xanthine-containing foods or beverages were allowed for 48 hours prior to dosing and until the last blood sample was collected for each study period. No medications known to affect lorazepam pharmacokinetics were allowed within 7 days prior to each study period or during any study period.

Vital signs consisting of blood pressure, respiratory rate, and pulse rate were measured at selected preset times throughout the study. Pulse oximetry monitoring was available for any volunteer who remained overly sedated for longer than 8 hours. Adverse events were recorded as they occurred. Subjects were specifically questioned about adverse events while vital signs were recorded. Nasal examinations to detect any local adverse reactions were performed by an otolaryngologist prior to study drug administration, 2 to 4 hours after administration, and at the poststudy evaluation.

Venous blood samples (10 ml) were collected from an indwelling catheter placed solely for study purposes. Samples were obtained at 0 (predose), 5, 15, 30, and 45 minutes and 1, 2, 3, 4, 8, 12, 18, 24, and 36 hours after lorazepam administration was completed. The samples, directly collected in Vacutainer® tubes containing sodium heparin, were separated into their respective plasma and cell components by a refrigerated centrifuge (4°C). The plasma was transferred to polypropylene tubes and stored at approximately –70°C.

Dose Administration

A standard 2.0 mg dose of lorazepam was used for all routes of administration. Subjects remained seated in bed at a 30- to 45-degree angle for 2 hours following

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each drug administration. For IV administration, 2.0 mg in 2.0 ml sterile solution was given at a rate of 0.5 ml/min over 4 minutes followed by 2.0 ml normal saline at a rate of 0.5 ml/15 seconds to flush the port. This resulted in a total infusion time of 5 minutes. The IV dose was administered in the arm contralateral to where the catheter was placed for blood withdrawal. IM lorazepam, 2.0 mg in 1.0 ml sterile solution, was administered as a single deep muscle injection into the frontal thigh area using standard techniques. Before IN administration, subjects gently blew their nose. Using the Pfeiffer unit dose spray pump (Pfeiffer of America, Princeton, NJ), a single spray of lorazepam (1.0 mg/100 µl) was administered to the lateral nasal wall of each nostril. Subjects were not allowed to blow their nose for 60 minutes following administration.

Assay of Samples

Sample analysis was conducted using a liquid chromatography/mass spectrometry/mass spectroscopy assay. The internal standard was deuterated lorazepam. Using 1.0 ml of human plasma, the lower limit of sensitivity was 0.10 ng/ml. The upper limit of detection was 25.0 ng/ml. Samples with concentrations greater than 25.0 ng/ml were diluted to a concentration between 0.10 and 25.0 ng/ml and reanalyzed. Coefficients of variation for within- and between-batch analysis were 0.0% to 11.1% and 4% to 10%, respectively. Accuracy was 90.0% to 110.0%.

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined using standard noncompartmental methods with log-linear least squares regression analysis to determine the elimination rate constants (WinNonlin, Pharsight Corp., Palo Alto, CA). The areas under the concentration versus time curves from time zero to infinity ($AUC_{0-\infty}$) were calculated by a combination of the linear and logarithmic trapezoidal rules, with extrapolation to infinity by dividing the last measurable serum concentration by the elimination rate constant (λ_z).[12] Values for the maximum concentration (C_{max}) and time to C_{max} (t_{max}) were determined by visual inspection of concentration versus time data for each subject. The elimination half-life was determined from $0.693/\lambda_z$. The absolute bioavailability (F) for the IN and IM dosage forms, assuming equal 2 mg doses, was determined by $F = AUC_{IN,0-\infty}/AUC_{IV,0-\infty}$ for the IN dose and $F = AUC_{IM,0-\infty}/AUC_{IV,0-\infty}$ for the IM dose. Clearance (CL for IV and CL/F for IN and IM doses) was determined by dividing the dose by $AUC_{0-\infty}$. Volume of distribution at steady state and for elimination (V_{ss} and V_z) were determined by moment curves.[13]

Statistical Considerations

Sample size was determined by clinical feasibility rather than standard calculations using alpha and power estimates. Posteriori statistical analysis was performed using an ANOVA model to evaluate sequence, subject (sequence), treatment, and period for carryover effects. Gender effects were also evaluated in the model. Log-transformed AUC and C_{max} values were used to calculate ratios and 90% confidence intervals (CI) for the three delivery routes. A p-value of < 0.05 was considered significant.

RESULTS

A total of 11 volunteers completed all study periods. Subject demographics are listed in Table I. Subject number 3 dropped out after the first dosing period due to personal reasons not related to the experimental procedures and subsequently was not included in any mean or pharmacokinetic calculations. The mean (*SD*) weight of the 11 completing subjects was 70.4 (8.7) kg. The age of subjects ranged from 20 to 26 years, with a mean of 22.0 years. All, except 1 subject, were Caucasian.

No significant adverse events occurred throughout the three study periods. A complete listing of side effects for each respective delivery route is provided in Table II. Overall, drowsiness/sleepiness was the most commonly reported effect. Pain at site of injection, "heavy" feeling, and blurred vision were also frequently noted during the study. Adverse events associated specifically with IN delivery included bad taste, cool feeling in the nose and throat, and a burning sensation. No local adverse reactions were detected in the nasal passage by the otolaryngologist. No clinically significant vital sign changes were observed during the entire study course.

The mean pharmacokinetic parameters for the IV, IM, and IN administrations are listed in Table III. The median t_{max} achieved for IM delivery was six times the t_{max} for IN delivery. The resulting C_{max} attained via IV administration was more than twofold greater than the C_{max} following IM or IN administration. The AUC_{0-t} and $AUC_{0-\infty}$ were both found to be larger for IV and IM delivery in comparison with the IN route. A mean bioavailability of 77.7% was observed for IN administration compared with the other routes (~100%).

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Table II Incidence of Adverse Events

Adverse Event	Number of Subjects with Complaint		
	IV	IM	IN
Back pain			1
Bad taste			6
Blurred vision	3		1
Burning/coolness in nose			8
Burning/coolness in throat			7
Ceiling moving	1		
Chemical smell			1
Dazed/confused	1		1
Diarrhea	1		
Disconnected/incoherent	1	1	1
Dizziness/lightheaded	4	3	2
Drowsiness/sleepiness	10	10	10
Euphoria/giddiness	1		2
Eyes heavy	1		
Eyes watery			11
Floating sensation	1		
Flu/cold-like symptoms		2	1
Groggy/heavy feeling	3		3
Headache	1	6	
Hiccups		1	2
Muscle tension/soreness	2	2	1
Nausea		2	1
Pain at injection site		5	
Pallor		1	
Phlegm in throat			1
Postnasal drainage		1	
Pulse elevated		1	
Relaxed	1	2	2
Slow response time		1	1
Thirsty	1		
Warm		1	

IV, intravenous; IM, intramuscular; IN, intranasal.

The average lorazepam concentration-time plots from 0 to 4 hours and 0 to 36 hours are shown in Figure 1. The plots for all three routes appear similar from 3 to 36 hours, suggesting the major differences occur during the first hours of administration. The rise in lorazepam plasma concentrations during the first hour is especially distinctive, with IV as the most rapid followed by IN and IM, respectively. The latter portion of the graph shows that IV and IM are fairly comparable in concentration magnitude while IN remains at a slightly lower level.

Following IN administration, a second absorption phase was detected in 5 subjects. Lorazepam appeared rapidly in the bloodstream initially after IN dosing. Within a time range of approximately 1 to 3.5 hours of the initial plasma concentration rise, another slight increase was observed. This is shown for 1 selected subject in whom the trend was well pronounced (Figure 2). The latter increase is most likely attributed to oral absorption from drug that passed into the pharynx area and was consequently ingested.

As determined by the ANOVA model, carryover effects for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were found to be insignificant. No significant gender differences were observed in C_{max}, but females were found to have significantly higher $AUC_{0\text{-}t}$ ($p = 0.0001$) and $AUC_{0\text{-}\infty}$ ($p = 0.0001$) values compared with males for all delivery routes. The ratios and 90% CI for IM/IV and IN/IV C_{max} parameters were very similar (Table IV). This was also reflected in the direct comparison of IN to IM, which resulted in CI of 0.72 to 1.24. AUC values for IN to both IV and IM ranged from 74% to 77% with low data variability, as evidenced by the relatively tight CI.

DISCUSSION

Pharmacokinetic parameters attained in the present study are comparable to values in the literature following administration of IV or IM lorazepam at an equivalent dose.[14-17] To our knowledge, only one other study has been conducted using IN lorazepam.[8] Lau and Slattery[8] administered a total lorazepam dose of 4 mg using a solution concentrated at 4 mg/100 µl. The dose was delivered via a pipette and was divided between each nostril. Their resultant parameters (mean [*SD*]) were as follows: C_{max} 18.7 (5.9), t_{max} range 0.5 to 4.0 hours, and bioavailability 51% (11.9). The parameters in the present study (Table III) are more favorable than previously reported. The C_{max} values observed from both studies are comparable even though the dose used by Lau and Slattery was twice the dose presently administered. In addition, their solution was four times more concentrated, and only half the volume was used for administration. Their bioavailability was approximately 24% lower, and the t_{max} range was much larger, suggesting slower, decreased uptake. In comparison, the present formulation and delivery device appear to provide faster, increased drug absorption.

Observation of the plasma concentration plots and calculated parameters indicate that IN delivery seems to primarily parallel IM delivery with exception to t_{max} and bioavailability. IN lorazepam reaches its maximum concentration at least two times faster than IM. However, IN has a bioavailability of approximately 78%, while IM bioavailability is practically 100%. The relatively small variation present in the pharmacokinetic

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