Acta Neurol Scand 2009: 120: 353–357 DOI: 10.1111/j.1600-0404.2009.01170.x

ACTA NEUROLOGICA
SCANDINAVICA

Clinical Commentary

Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers

Ivaturi VD, Riss JR, Kriel RL, Cloyd JC. Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers.
Acta Neurol Scand 2009: 120: 353–357.

Objective – The purpose of this pilot study was to determine the pharmacokinetics and tolerability of an investigational diazepam (DZP) formulation and a parenteral midazolam (MDZ) formulation following intranasal (i.n.) administration for the efficient treatment of seizure emergencies. *Methods* – Each subject received 5 mg of DZP and MDZ via both i.n. and intravenous routes in a four-way, randomized crossover trial. Blood samples were collected over 48 h. DZP and MDZ concentrations were measured using HPLC. Using analog scales, subjects rated tolerability (0 = no change from normal; 10 = maximum intolerability) and pain (0 = no pain; 4 = extreme pain) prior to and 0, 5, 15, 60 min, and 8 h after administration. *Results* – The C_{max} and T_{max} values for i.n. DZP and MDZ were 179.2 ng/ml and 28.8 min vs 62.8 ng/ml and 21.6 min, respectively. Immediately following i.n. administration, subjects reported tolerability scores of 6.75 and 6.0, and identical pain scores, 3.2, for DZP and MDZ, respectively. *Conclusion* – Both formulations were rapidly absorbed following i.n. administration with transient discomfort. DZP had a longer half-life, which may result in an extended duration of action. Further studies in large patient populations to evaluate the safety after long term use, efficacy and pharmacokinetics of i.n. DZP are warranted.

V. D. Ivaturi[1,2], J. R. Riss[1], R. L. Kriel[1,2], J. C. Cloyd[1,2]

[1]Center for Orphan Drug Research and [2]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN, USA

Key words: diazepam; intranasal; midazolam; pharmacokinetics; tolerability

Vijay D. Ivaturi, Center for Orphan Drug Research, Rm 4-206, McGuire Translational Research Facility, 2001 6th St. SE, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA
Tel.: 612 624 1861
Fax: 612 626 9985
e-mail: ivatu001@umn.edu

Presented as a poster at the American Academy of Neurology, April 2006, 'Bioavailability and tolerability of a novel intranasal diazepam formulation in healthy volunteers'.

Accepted for publication January 5, 2009

Introduction

Individuals with uncontrolled epilepsy represent one of the greatest challenges in the management of this disorder (1, 2). These patients are particularly prone to status epilepticus (SE) as well as prolonged or cluster seizures which are in themselves serious conditions that can evolve into SE (3). Intravenously administered benzodiazepines (BZDs) are widely used for the treatment of seizure emergencies. When given within 30 min of seizure onset, intravenous (i.v.) BZDs are effective in more than 80% of patients (3, 4). However, i.v. administration requires skilled personnel and transport to a medical facility which can delay initiation of therapy (5). Treatment delay is associated with longer seizure duration, greater difficulty in terminating the seizure, prolonged hospitalization, higher mortality, and reduced quality of life (3, 6).

Administration of BZDs by other routes could permit earlier initiation of therapy outside of medical facilities. Rectal administration of diazepam (DZP) for the treatment of seizure emergencies is safe and effective, reduces medical costs, and improves quality of life, but many patients and their caretakers are reluctant to consider this mode of therapy especially when the patient is in a location which is socially embarrassing (7–10).

The availability of a fast-acting intranasal (i.n.) treatment that can be easily administered by the

patient or a caregiver would greatly improve the management of seizure disorders. Essential characteristics for an i.n. drug delivery system in the treatment of seizure emergencies include: patients must be able to tolerate the formulation; administration volume of 0.5 ml or less; rapid, consistent absorption; and easy administration by non-medical caregivers and patients.

The purpose of this study was to evaluate the pharmacokinetics and tolerability of i.n. administered DZP and midazolam (MDZ) in healthy adult volunteers.

Methods

The study was approved by the Institutional Review Boards at the University of Minnesota and Hennepin County Medical Center. Four healthy, non-pregnant women aged 20–24 years participated in the study. Subjects provided informed consent and were compensated for participation. Subjects were excluded if they were in poor health, unwilling or unable to receive i.n. or i.v. medications, pregnant, smokers, allergic to DZP or MDZ, or had narrow-angle glaucoma.

Subjects' treatment sequence was randomly assigned using a latin-square design. The study consisted of a four-way, randomized, single-blind, crossover design in which subjects received 5 mg doses of i.n. DZP, i.n. MDZ, i.v. DZP and i.v. MDZ. Subjects were admitted to the clinical research unit located at Hennepin County Medical Center and remained there for 8 h on four separate occasions after a minimum 1-week washout period.

Commercial formulations were used for i.v. administration of DZP and MDZ. The i.n. DZP formulation consisted of an investigational supersaturated solution containing 40 mg/ml of DZP, glycofurol and water. The injectable MDZ formulation (5mg/ml) was also used for i.n. administration. The i.n. doses of 5 mg were administered using a 1.0 ml syringe such that 0.125 ml of the DZP solution and 1 ml of the MDZ solution were dripped slowly into either one of the nostrils. Intranasal administration of normal saline (0.5 ml) given with a 1.0 ml dropper served as a control to compare tolerability of the drugs. Using a 10-point Global Tolerability Analog Scale, each subject rated overall tolerability of the i.n. (drug and normal saline) and i.v. doses (drug only) at 5 min prior to and 0, 5, 15, 60 min and 8 h after drug administration. A score of 10 was considered the least tolerable. This scale is analogous to Visual Analog Scales and has been adapted from a previous study evaluating the tolerability of a nasal formulation (11). Subjects also completed a pain and subjective discomfort questionnaire for the i.n. administrations. Using a 4 point analog scale with 4 representing extreme pain or discomfort, subjects rated specific pain characteristics: burning, stinging, and throbbing at −15, 0, 5, and 15 min.

Blood samples of 5 ml for pharmacokinetic analysis were collected, by means of a catheter inserted into a forearm vein, into glass tubes containing ethylenediamine tetraacetic acid as anticoagulant at −5, 0, 1, 5, 10, 20, 30, 60 min and 8 h. For DZP, additional samples were obtained at 24 and 48 h. Within 15 min of collection, the blood samples were spun in a centrifuge, and plasma was carefully separated. Plasma samples were stored at −80°C pending analysis.

Drug assay

Plasma samples were analyzed for MDZ and DZP concentrations using an Agilent 1100 series HPLC system (Agilent Technologies, Palo Alto, CA, USA) with a C4 column. The mobile phase for the system consisted of 40% acetonitrile and 60% phosphate buffer (pH-6.0). The flow rate of the mobile phase was 0.5 ml/min and the injection volume was 50 µl. Standard curves were prepared over the range of 5–500 ng/ml and quality control samples containing 15 (low), 50 (medium) and 250 ng/ml (high) of DZP and MDZ were prepared separately with blank human plasma.

An aliquot of 0.2 ml of the plasma was added to a 12 × 75 mm glass tube. A sample of NaOH (200 µl) and the internal standard lorazepam (200 µl) were added and the solution was mixed well. A 2 ml volume of ether was poured in the tube as an extracting solvent and vortex mixed for 1 min and then centrifuged for 10 min at 769 *g*. A sample of the organic layer was collected and evaporated until dry with nitrogen at 34°C, and then 200 µl of the HPLC mobile phase was added to dissolve the residue. After 30 s of vortex mixing, 50 µl of the sample solution was injected into the HPLC system.

The standards for DZP and MDZ were analyzed on separate days and the mean coefficients of variation were 5.6% and 5.0%, respectively. The mean coefficients of variation for the intraday variation of DZP and MDZ quality control samples were 8.6% and 7.5%, respectively.

Pharmacokinetic analysis

Concentration–time data of DZP and MDZ were examined using non-compartmental pharmacokinetics analysis with WinNonLin software (version 5.2; Pharsight Corporation, Mountain View, CA,

Table 1 Mean (±SD) pharmacokinetic parameters of diazepam (DZP) and midazolam (MDZ) in healthy volunteers following intravenous (i.v.) and intranasal (i.n.) administration of 5 mg dose

PK parameter	i.v. DZP	i.n. DZP	i.v. MDZ	i.n. MDZ
T_{max} (min)	–	28.8 ± 20.96	–	21.6 ± 7.63
C_{max} (ng/ml)	344.0 ± 92.81*	179.2 ± 8.85	165.2 ± 96.42*	62.8 ± 14.51
Half-life (h)	59.1 ± 7.76	22.4 ± 3.45	0.9 ± 0.60	3.0 ± 0.74

*Concentration 5 min after injection.

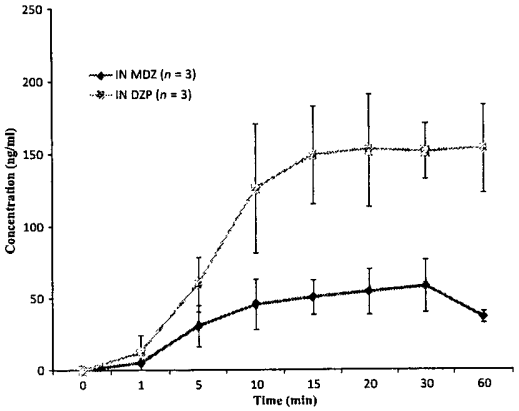

Figure 1. Comparison of mean intranasal diazepam and midazolam concentration vs time profile.

USA). The terminal rate constant (λz) was determined from the slope of the terminal log-linear portion of the plasma–concentration–time curve, and the terminal half-life ($t_{1/2}$) was calculated as $\ln 2/(\lambda z)$. Maximum plasma concentrations (C_{max}) and time to maximum concentration (T_{max}) were determined by direct observation of the data. Means and standard deviations for the parameters were also obtained using the descriptive statistics tool in WinNonlin version 5.2.

Results

Four women, aged 20–24 years entered the study. One subject dropped out due to travel conflicts after completing the i.n. DZP arm and was excluded from all group analyses. The pharmacokinetic parameters for the three subjects are summarized in Table 1. The mean concentration–time profiles are shown in Fig. 1 and the individual subject's concentration time profiles for both i.n. DZP and MDZ are shown in Fig. 2. The average i.n. DZP C_{max} and T_{max} were 179.2 ± 8.8 ng/ml and 28.8 ± 20.9 min, respectively. The average i.n. MDZ C_{max} and T_{max} were 62.8 ± 14.5 ng/ml and 21.6 ± 7.6 min, respectively. The C_{max} and T_{max} of the subject who dropped out of the study were 109.48 ng/ml and 20 min, respectively following i.n. DZP administration.

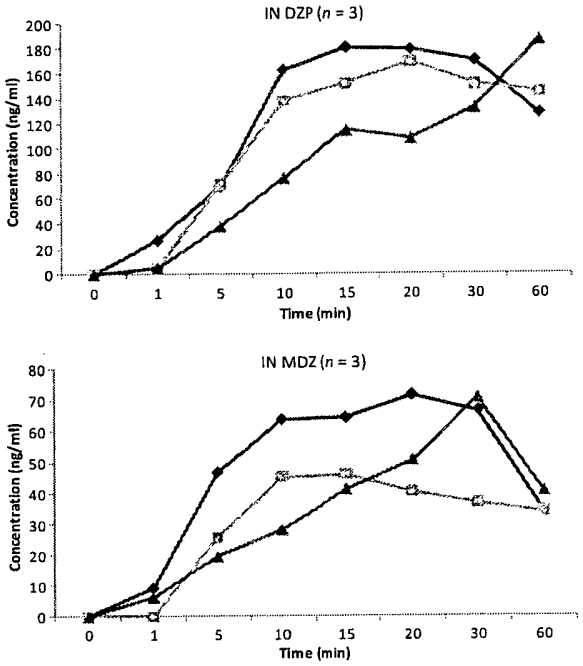

Figure 2. Concentration time profiles (0–60 min) of individual subjects (n = 3) for intranasal midazolam and diazepam.

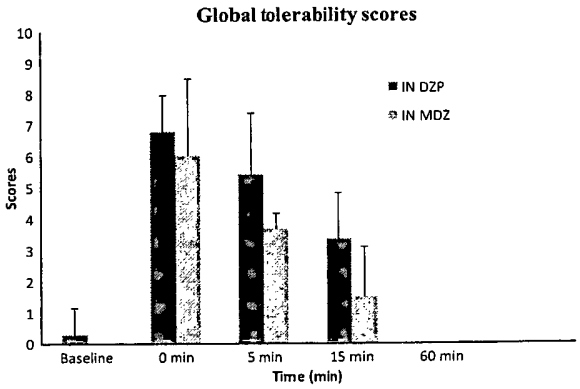

Figure 3. Comparison of mean global tolerability scores after intranasal administration (n = 3).

Immediately following i.n. administration, subjects reported an average global tolerability score of 6.75 and 6.0 for DZP and MDZ, respectively, which were statistically not different ($P > 0.05$) (Fig. 3). Within 15 min, scores decreased to 3.3 and 1.5, respectively, which eventually returned to baseline (Fig. 3).

Subjects rated both formulations as causing considerable pain with a maximum score of 3.2 immediately following nasal administration. Fifteen minutes later, the mean pain score for both drugs was 1.2. Posterior nasal drainage and watery eyes were reported by all subjects.

Discussion

Using PubMed with key terms 'intranasal midazolam and diazepam', we found no published reports directly comparing i.n. DZP and i.n. MDZ. Various MDZ formulations given i.n. have been investigated with most studies using the commercially available injectable MDZ solution (12, 13). These studies with doses between 10–20 mg (2–4 ml) reported C_{max} and T_{max} values in the range of 147–192 ng/ml and 14–25 min, respectively. The absorptive area of the nose limits the volume administered to approximately 0.1–0.3 ml per nostril although smaller volumes are preferable (14). When the commercially available injectable MDZ solution is given i.n., volumes exceeding 0.20 ml are required in order to administer a clinically relevant dose (12). This could affect both bioavailability and C_{max}. Highly concentrated investigational nasal MDZ formulations, including a water and propylene glycol admixture (pH 4) (15), and a solution containing 14% (w/v) sulfobutylether β-cyclodextrin (pH 4.3) (16) have also been studied in humans. Although these formulations permit administration of smaller volumes (0.2–0.3 ml), there was no distinguishable difference in the values of C_{max} and T_{max}.

Three previous studies have investigated i.n. DZP in humans. Gizurarson et al. compared an i.n. 2 mg dose of a 20 mg/ml DZP solution dissolved in 5% glycofurol in polyethylene glycol 200 with the same dose given i.v. (17). Blood samples were collected for 5 h following drug administration. The mean bioavailability was 50.4 ± 23.3% with a time to peak concentration of 18 ± 11 min. All subjects complained of nasal discomfort immediately following drug administration, but the discomfort resolved within 30 min. Lindhardt et al. evaluated an i.n. formulation of DZP in polyethylene glycol 300 in seven healthy volunteers. Using a crossover design, they compared 4 and 7 mg i.n. doses with a 5 mg i.v. dose and collected blood samples for 60 min after drug administration. The i.n. formulation had a relative bioavailability of 45% and 42%, a C_{max} of 99 and 179 ng/ml and a T_{max} of 18 and 42 min for the 4 and 7 mg doses, respectively (18). Given that the half-life of DZP ranges from 24 to 48 h, their bioavailability values are likely an underestimate of the actual extent of absorption. Lau and Slattery, using a 10 mg dose of DZP dissolved in Cremophor EL, reported a bioavailability of 78% with a C_{max} of 175 ng/ml and a T_{max} of 1 h (19). A recent study by Cloyd et al. (20) determined the pharmacokinetics and dose proportionality of 5 and 10 mg doses of an i.n. administered DZP formulation compared with i.v. administration in eight healthy volunteers using a crossover design. The formulation used was a 40 mg/ml supersaturated solution of DZP in glycofural–water cosolvent mixture. Each subject received two i.n. and one i.v. dose of DZP and blood samples were collected up to 48 h after dosing. The mean C_{max}, T_{max} and $t_{1/2}$ were 134.3 ±61.9 ng/ml, 55.6 ± 60.3 min, and 49.1 ± 20.4 h for the 5 mg dose, and 247.0 ± 60.9 ng/ml, 39.3 ± 38.1 min, and 57.0 ± 28.0 h for the 10 mg dose. Using analog scales, subjects rated tolerability (0 = no change from normal; 10 = maximum intolerability) prior to and 0, 5, 15, 60 min, and 8 h after administration. The mean tolerability scores observed were 4.4 and 4.7 for the 5 and 10 mg doses. Both these scores dropped down to 3 and 2.5, 15 min post-dose and to 1, 60 min post-dose.

The pharmacokinetic parameters for i.v. DZP and i.v. MDZ shown in Table 1 are comparable to those reported in the literature (21). The relationship between DZP pharmacokinetics and pharmacodynamics is complex. Following rapid i.v. administration, relatively high plasma DZP concentrations occur prior to distribution to various body compartments including the central nervous system (CNS). This makes correlation of DZP levels with seizure control difficult. In contrast, the absorption of DZP following rectal or nasal administration, although relatively rapid, does permit equilibration of DZP concentrations between plasma and the CNS. Milligan et al. rectally administered a 20 mg dose of DZP solution or placebo to 10 adults with epilepsy and then observed spike wave activity and measured plasma concentrations. Rectal DZP significantly reduced EEG spike frequencies within 20 min at a mean serum DZP level of 210 ng/ml. The mean C_{max} of DZP was 413 ng/ml and the mean T_{max} was 32 min (22). Based on these results, subsequent controlled clinical trials using similar doses, and presumably similar plasma DZP concentrations, have demonstrated that rectal DZP is effective in treating acute repetitive seizures (8).

Although we administered 5 mg DZP i.n. in this study, doubling the dose to 10 mg by giving 5 mg DZP into each nostril should result in concentrations >200 ng/ml that are attained within 5–10 min.

It is unclear whether prolonged serum DZP concentrations are needed to achieve and maintain seizure control. The longer elimination half-life of DZP compared with MDZ as shown in the results conveys a theoretical advantage in preventing subsequent seizure recurrence. In controlled investigations DZP is effective in treatment of seizure emergencies (8, 23). Such studies have yet to be conducted with MDZ.

All subjects reported moderate discomfort with both formulations. This is a major limitation of both the injectable MDZ solution and the investigational DZP formulation.

Measures to improve comfort level or tolerability are needed for greater patient acceptance. Nonetheless, some patients and caretakers would prefer the transient discomfort of the present i.n. formulations to rectal administration of medication in public settings. Similar views have been expressed in a comparative study of i.n. MDZ and rectal DZP (10). Intranasal DZP may be useful in the treatment of seizure emergencies. However, this was a small study of healthy volunteers which precludes generalization to clinical use and further research is needed to improve tolerability of the formulation and to characterize the appropriate dose.

Acknowledgements

We thank Dennis Weller for helping with the HPLC analysis. Funding for this study was generously provided by Parents Against Childhood Epilepsy (PACE) and the Epilepsy Foundation.

References

1. Dodson WE. Epilepsy, Cerebral Palsy and IQ. In: Pellock JM, Dodson WE, Bourgeois BFD, eds. Pediatric Epilepsy, Diagnosis and Therapy, 2nd edn. New York: Demos, 2001; 613–27.
2. Shinnar S, Maytal J, L K. Recurrent status epilepticus in children. Ann Neurol 1992;**31**:598–694.
3. Lowenstein D, Alldredge B. Status epilepticus. N Engl J Med 1998;**338**:970–6.
4. Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurol Scand 2008;**118**:69–86.
5. Jordan K. Status epilepticus. A perspective from the neuroscience intensive care unit. Neurosurg Clin N Am 1994; **5**:671–86.
6. Alldredge B. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995;**12**:213–6.
7. O'Dell C, Shinnar S, Ballaban-Gil KR et al. Rectal diazepam gel in the home management of seizures in children. Pediatr Neurol 2005;**33**:166–72.
8. Driefuss F, Rosman N, Cloyd J et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998;**338**:1869–75.
9. Kriel R, Cloyd J, Hadsall R, Carlson A, Floren K, Jones-Saete C. Home use of rectal diazepam for cluster and prolonged seizures: efficacy, adverse reactions, quality of life and cost analysis. Pediatr Neurol 1991;**7**:13–7.
10. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. Pediatr Neurol 2006;**34**:355–9.
11. Dingemanse J, Soubrouillard C, Paris J, Pisano P, Blin O. Pronounced effect of caprylocaproyl macrogolglycerides on nasal absorption of IS-159, a peptide serotonin 1B/1D-receptor agonist. Clin Pharmacol Ther 2000;**68**: 114–21.
12. Burstein AH, Modica R, Hatton M, Forrest A, Gengo FM. Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. J Clin Pharmacol 1997;**37**: 711–8.
13. Bjorkman S, Rigemar G, Idvall J. Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. Br J Anaesth 1997;**79**:575–80.
14. Romeo VD, deMeireles J, Sileno AP, Pimplaskar HK, Behl CR. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Adv Drug Deliv Rev 1998;**29**:89–116.
15. Knoester PD, Jonker DM, Van Der Hoeven RT et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol 2002;**53**: 501–7.
16. Loftsson T, Gudmundsdottir H, Sigurjonsdottir JF et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm 2001;**212**: 29–40.
17. Gizurarson S, Gudbrandsson F, Jonsson H, Bechgaard E. Intranasal administration of diazepam aiming at the treatment of acute seizures: clinical trials in health volunteers. Biol Pharm Bull 1999;**22**:425–7.
18. Lindhardt K, Gizurarson S, Stefansson SB, Olafsson DR, Bechgaard E. Electroencephalographic effects and scrum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers. Br J Clin Pharmacol 2001;**52**:521–7.
19. Lau S, Slattery J. Absorption of diazepam and lorazepam following intranasal administration. Int J Pharm 1989; **54**:171–4.
20. Ivaturi V, Riss J, Kriel R, Cloyd J. Bioavailability and tolerability of intranasal diazepam in healthy adult volunteers. Epilepsy Res. 2009, in press.
21. Anderson GD, Miller JW. Benzodiazepines; chemistry, biotransformation, and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, eds. Antiepileptic drugs, 5 edn. Philadelphia: Lippincott Williams & Wilkins, 2002;187–206.
22. Milligan N, Dhillon S, Oxley J, Richens A. Absorption of diazepam from the rectum and its effect on interictal spikes in the EEG. Epilepsia 1982;**23**:323–31.
23. Kriel RL, Cloyd JC, Pellock JM, Mitchell WG, Cereghino JJ, Rosman NP. Rectal diazepam gel for treatment of acute repetitive seizures. The North American Diastat Study Group. Pediatr Neurol 1999;**20**:282–8.