Epilepsy Research (2009) **84**, 120—126

journal homepage: www.elsevier.com/locate/epilepsyres

Bioavailability and tolerability of intranasal diazepam in healthy adult volunteers

Vijay D. Ivaturi[a,b,*], **Jennifer R. Riss**[a], **Robert L. Kriel**[a,b,c], **Ronald A. Siegel**[d], **James C. Cloyd**[a,b]

[a] *Center for Orphan Drug Research, University of Minnesota, United States*
[b] *Department of Experimental and Clinical Pharmacology, United States*
[c] *Departments of Neurology and Pediatrics University of Minnesota, United States*
[d] *Department of Pharmaceutics, University of Minnesota, United States*

Received 10 July 2008; received in revised form 2 December 2008; accepted 11 January 2009
Available online 20 February 2009

KEYWORDS
Seizure emergencies;
Intranasal therapy;
Diazepam;
Glycofurol;
Out-of-hospital

Summary Intranasal therapy has been proposed as an alternative for the management of seizure emergencies. The bioavailability, dose proportionality and tolerability of a supersaturated intranasal formulation of diazepam (DZP) solubilized in a glycofurol—water cosolvent system was investigated. Eight healthy volunteers were randomized into a single-blind, three-way crossover study to compare 5 and 10 mg intranasal DZP doses of the investigational formulation with a 5 mg dose of a DZP solution (DZP injectable, 5 mg/mL) administered intravenously. Treatments were separated by a two-week washout period. Plasma samples for DZP analysis were collected pre-dose and at regular intervals up to 48 h post-dose and assayed by HPLC. Visual analog scales (VAS) were used to assess tolerability (1-tolerable; 10-extremely intolerable) and pain (1-no pain; 4-extreme pain) at predefined time points. Following the 5 and 10 mg doses, the median t_{max} were 20 and 30 min and the mean C_{max} were 134.3 ± 62 and 247.6 ± 61 ng/mL. Estimated bioavailability was 75% for both doses. Pain scores of 2 and 2.3 were observed following the 5 and 10 mg doses; tolerability scores were 4.4 and 4.7. Pain and tolerability scores returned to baseline within 10 h. Our formulation provided reasonable bioavailability, but was not well tolerated.

Introduction

Frequently recurring seizures, prolonged seizures or status epilepticus are recognized as seizure emergencies (Pellock, 2007). Rapid treatment of such emergencies improves outcomes and minimizes associated morbidity (Alldredge et al., 2001). The standard approach to treating seizure emergen-

* Corresponding author at: Center for Orphan Drug Research, Rm 4-226, McGuire Translational Research Facility, 2001 6th St. SE, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA. Tel.: +1 612 624 1861; fax: +1 612 626 9985.
E-mail address: ivatu001@umn.edu (V.D. Ivaturi).

0920-1211/$ — see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2009.01.001

cies is intravenous administration of antiseizure medications in an emergency center. There is now substantial evidence that the use of an out-of-hospital medication to terminate repeated or prolonged seizures reduces visits to the emergency department, lowers medical costs, and improves quality of life (O'Dell et al., 2005, 2007; Driefuss et al., 1998; Kriel et al., 1991).

Benzodiazepines are widely used in the treatment of seizure emergencies. When there is intravenous access, lorazepam is considered the drug of choice for the treatment of prolonged seizures and status epilepticus (Lowenstein and Alldredge, 1998). However, in the management of seizure emergencies outside a hospital setting, rectal administration of diazepam has been employed with good success. Although buccal and intranasal administration of benzodiazepines are used in clinical practice, only rectal diazepam has been shown to be safe and effective in terminating acute repetitive seizures in blinded, placebo-controlled studies (Driefuss et al., 1998; Cereghino et al., 1998). Nonetheless, older children and adults often refuse therapy because of social objections to this route of administration (Tatum, 2002; O'Regan et al., 1996; Wilson et al., 2004). Hence, many patients are effectively without benefit of an approved therapy that can be administered outside the hospital.

Availability of a fast acting intranasal treatment that can be easily administered by the patient or a caregiver would greatly improve the management of out-of-hospital seizure emergencies. Essential characteristics for an intranasal drug delivery system include a well-tolerated formulation; administration volume of $\leq$0.3 mL (approximately 100—150 μL/spray/nostril); rapid, consistent absorption; and easy administration by non-medical caregivers and patients. Nasal drug delivery is well accepted as a mode of therapy for treatment of seizure emergencies (Bhattacharyya et al., 2006). Benzodiazepines, especially midazolam, given intranasally have been studied in several open-label trials. These studies provide evidence that they can be easily administered, are reasonably safe, and exhibit a clinical effect comparable to rectal diazepam (Bhattacharyya et al., 2006; Scheepers et al., 2000; Lahat et al., 2000).

Relative to other benzodiazepines, diazepam (DZP) has certain physicochemical and pharmacological characteristics such as high lipid solubility and a long elimination half life that support its use in intranasal therapy (Cloyd, 2007). Our group has developed an investigational intranasal formulation of DZP. In this formulation, DZP dissolved in glycofurol is rapidly mixed with water, which is a poor solvent of DZP but is fully miscible with glycofurol. With proper care, the result is a supersaturated DZP solution that is thermodynamically unstable but kinetically stable for several tens of minutes. In the supersaturated state, DZP has a high activity, and is expected to be rapidly absorbed across the nasal mucosal membrane (Hou and Siegel, 2006).

The objective of the present study was to carry out a randomized, single-blind, three-way crossover study, to determine the bioavailability and pharmacokinetics of an investigational formulation of DZP administered intranasally at 5 and 10 mg as compared to a 5 mg intravenous dose. Safety and tolerability of this investigational intranasal formulation were also evaluated.

Methods

Subjects and study design

Subjects were healthy volunteers 18 years or older who provided informed consent and were compensated for participation. Subjects were excluded if they were in poor health, unwilling or unable to receive intranasal or intravenous medications, pregnant, smokers, allergic to DZP, or had narrow-angle glaucoma. The study was approved by the Institutional Review Boards at the University of Minnesota and Hennepin County Medical Center and was conducted at DaVita Clinical Research Unit (CRU) in Minneapolis.

The study utilized a randomized, single-blind, three-way crossover design to compare the pharmacokinetics and tolerability of a commercially available parental DZP administered intravenously (5 mg) and two intranasal DZP doses (5 mg and 10 mg). This investigation was intended to serve as a pilot study to characterize the tolerability and pharmacokinetics of a saturated glycofurol formulation. We chose a sample size which would give us sufficient data to do exploratory analysis and understand the performance of the formulation. The sample size was based on the ability to detect a 30% difference in AUC between nasal and intravenous administration, assuming one drop-out (Power = 90%, α = .05). Eight subjects received the two intranasal and one intravenous dose of DZP with a two-week washout period between doses. Prior to each of the three treatments, the subject's eligibility was reviewed. Subjects were instructed to abstain from prescription or over-the-counter medications beginning 24 h prior to each admission through each 48 h blood draw. They were also instructed to not consume alcoholic beverages 24 h before and after drug administration study days. Subjects were admitted to the CRU where they would remain for 10 h.

On the morning of the first day of the study, subjects were randomized to receive a 5 mg intranasal, or 10 mg intranasal, or 5 mg intravenous dose of DZP. Subjects were blinded to the dose of the intranasal treatment, as both doses involved administration into two nostrils. For the 5 mg dose, a control solvent was administered in the second nostril whereas for the 10 mg dose, subjects received 5 mg of the formulation in each nostril to maintain the blind and study conditions. Each subject had an indwelling catheter placed in her/his arm. All doses were administered while the subjects were in the supine position.

Study drugs

The intravenous formulation used in this study was the commercially available parental DZP (diazepam injectable, 5 mg/mL, USP). The intravenous drug was acquired by the CRU. The injectable DZP was stored as per the approved labeling in a secure location.

The intranasal DZP formulation was a freshly prepared supersaturated solution containing 40 mg/mL DZP in a 60—40% (v/v) cosolvent mixture of glycofurol and water (Hou and Siegel, 2006). The intranasal dose was administered as 5 mg dose (0.125 mL) using a 1-mL syringe, with the subject lying in the supine position such that the 5 mg dose was instilled in one nostril, with a cosolvent blank of equal vol-