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A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers

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Summary Diazepam rectal gel (Diastat®) is the only FDA-approved product indicated for acute repetitive seizures. Despite its proven efficacy, most older children and adults object to this route of administration. As a result, many patients do not realize the benefit of a therapy that can improve outcomes and decrease healthcare costs. Intranasal administration of benzodiazepines offers a potential alternative. The primary objective of this study was to compare the bioavailability and pharmacokinetics of two novel intranasal (IN) diazepam (DZP) formulations versus intravenous (IV) administration in healthy volunteers. Twenty-four healthy volunteers were randomized into an open-label, three-way crossover study. 10 mg doses of two investigational intranasal DZP formulations (solution, suspension) and a 5 mg IV dose of commercially available DZP injectable, USP were given. A two-week washout period separated treatments. Plasma samples for DZP analysis were collected pre-dose and at regular intervals up to 240 h post-dose. DZP concentration—time data were analyzed using a non-compartmental pharmacokinetics approach. Exposure following administration of DZP IN solution (absolute bioavailability — 97%) was greater than the IN suspension (absolute bioavailability — 67%). Mean C_{max} values for the suspension and solution formulations were 221 ng/mL and 272 ng/mL, respectively. Median time to maximum concentration (T_{max}) was 1 h and 1.5 h for suspension and solution formulation, respectively. Both investigational intranasal formulations were well tolerated. The results of this pilot study indicate that development of an intranasal diazepam formulation with high bioavailability, reasonable variability, and good tolerability is feasible.

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Introduction

Seizure emergencies are associated with high morbidity and mortality which can be reduced by prompt and appropriate pharmacological therapy. During a seizure, there is an increased release of excitatory neurotransmitters, usually glutamate and/or aspartate. Normally, an increase of the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) will result in cessation of the seizure (Dalby and Mody, 2001). However, if GABA is not released promptly, excess excitation may lead to loss of neural control and convulsive seizures. In 1993, Epilepsy Foundation of America's Working Group on Status Epilepticus recommended that antiepileptic drug administration should be initiated whenever a seizure has lasted 10 min (Working Group on Status Epilepticus, 1993). A recent review article suggested that most epileptic seizures last 1—4 min and seizures lasting greater than 5 min should be treated as status epilepticus (Kälviäinen et al., 2009). Evidence suggests that the longer a seizure continues, the less likely it is to spontaneously stop (Shinnar et al., 2008) and can also progress to status epilepticus, which is associated with increased morbidity and mortality, suggesting a need for prompt therapy (Lowenstein et al., 1999).

The standard treatment for seizure emergencies is intravenous administration of benzodiazepines, usually lorazepam or diazepam followed by phenytion or fosphenytoin (Lowenstein and Alldredge, 1998). Although intravenous route is the most effective option for quick cessation of seizures, therapy gets delayed as it requires skilled medical personnel and transportation to medical facility. Diazepam rectal gel (Diastat®) is the only formulation of diazepam indicated for the out-of-hospital management of selected, refractory patients who require intermittent use of diazepam to control bouts of increased seizure activity such as acute repetitive seizures. Introduction of rectal diazepam products in Europe and in the United States dramatically changed the management of seizure emergencies. With these formulations, caregivers were able to achieve good outcomes by initiation of early treatment after the onset of acute repetitive and prolonged seizures. As a result, emergency department admissions have declined with a decrease in health care costs and improved quality of life (Kriel et al., 1991). Nonetheless, social objections by older children and adults and legal concerns about rectal administration have limited its use. As a result, many patients do not realize the benefit of a therapy that can improve outcomes and decrease healthcare costs. Shortly after the introduction of rectal diazepam, a need for alternative route of administration was realized and interest emerged to investigate and develop different formulations of benzodiazepines (clonazepam, diazepam, lorazepam, and midazolam) using one or more routes of administration such as buccal, intramuscular and nasal.

Intranasal benzodiazepines appear to be particularly promising and several research groups carried out studies to investigate the pharmacokinetics, bioavailability and tolerability (Lau and Slattery, 1989; Burstein et al., 1997; Wermeling et al., 2001, 2006, 2009; Knoester et al., 2002; Dale et al., 2006; Ivaturi et al., 2009; Haschke et al., 2010; Veldhorst-Janssen et al., 2011; Anderson et al., 2012; Hardmeier et al., 2012). To meet the need of an alternate therapy for seizure emergencies, our group has investigated several intranasal formulations of diazepam. Our earlier studies have demonstrated the feasibility of nasal administration of diazepam (Ivaturi et al., 2009). Diazepam was absorbed rapidly following nasal administration and the pharmacokinetic profile of intranasal formulations compared favorably to that of the rectal diazepam gel. However, the tolerability was only moderate. The results of earlier studies concluded that intranasal diazepam offers a viable alternative to rectal administration, however further enhancement of formulations was needed to both improve tolerability and the extent and consistency of absorption. In the current study, two novel formulations of diazepam nasal spray have been evaluated and compared with intravenous administration. The primary objective of this study was to assess the bioavailability and pharmacokinetics (PK) of diazepam after intranasal administration of solution and suspension formulations in healthy volunteers under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of these two diazepam nasal spray formulations after a single administration.

Methods

Subjects and study design

Subjects were healthy volunteers 18—45 years old with BMI between 19 and 30 kg/m^2, who provided informed consent and were compensated for participation. Subjects with known history of severe seasonal or non-seasonal allergies, having nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration were excluded. Subjects who were pregnant or lactating, smoking or using tobacco products within the 6 months prior to the first dose of the study drug, allergic to diazepam, or have been on restrictive diet were also excluded. The study was approved by the Institutional Review Boards at the University of Minnesota and was conducted at PRISM Clinical Research Unit (CRU) in St. Paul, MN. The principal investigator was present at the CRU during and following drug administration.

The study utilized a randomized, open-label, six sequence, three-way crossover design to compare the pharmacokinetics and bioavailability of a commercially available parenteral DZP administered intravenously (5 mg) with two novel intranasal DZP formulations (10 mg). Twenty four 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 drugs and over the counter medications, 14 days and 7 days prior to the first dose of study, respectively. Treatment with any known enzyme altering drugs such as barbiturates, phenothiazines, cimetidine, carbamazepine, within 30 days prior to the first dose of study drug or during the study was also one of the exclusion criteria. Subjects were admitted to the study unit no later than 1900 h of the evening prior to study drug administration. The next morning, following an overnight fast, subjects were randomized to receive 10 mg intranasal dose of DZP solution, or 10 mg intranasal dose of