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A pharmacokinetic and pharmacodynamic study, in healthy volunteers, of a rapidly absorbed intranasal midazolam formulation

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Summary
Purpose: To compare 2.5 mg and 5.0 mg single-dose pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of an intranasal (IN) midazolam formulation, to a 2.5-mg intravenous (IV) dose.
Methods: Design was an open-label, three-way crossover, randomized PK and PD study in seventeen healthy volunteers. Twelve-hour PK parameters were determined for each treatment arm. Subjects completed serial self-ratings for sedation and other drug effects. Nurse observers made serial observations for sedation and adverse effects. An otolaryngologist conducted a nasal endoscopy, pre-dose, 2—4 h, and at end of study, to examine the nasal cavity for formulation-induced changes in nasal anatomy.
Results: Midazolam was rapidly absorbed following IN administration, with a median t_{max} of 10 min; dose proportionate increases for C_{max} and AUC; $t_{1/2}$ of 4 h; and, 60% (±23) nasal administration bioavailability compared to the IV dose. PD responses were rapid, paralleled the PK, and in magnitude was in a rank order of IV 2.5 mg ≥ IN 5.0 mg > IN 2.5 mg doses. The formulation was well tolerated with no serious cardiovascular or respiratory complications. Fourteen subjects complained of at least one of the following: a brief and mild to moderate intensity facial flushing, nasal passage burning, sore throat or bad taste after drug administration. There were no adverse findings from the nasal endoscopic exam.
Conclusion: Dosages of an investigational IN midazolam formulation resulted in rapid absorption and attained plasma concentrations that correlated with pharmacodynamic effects.

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1. Introduction

Acute isolated seizure lasting longer than 5 min, repetitive or recurrent seizures and status epilepticus are all deemed medical emergencies (Pellock, 2007). Mortality and worse neurologic morbidity are directly associated with the duration of seizure activity (Logroscino et al., 2001; Shinnar et al., 2001; Claasen et al., 2002; Feen et al., 2008; Wang et al., 2008; Stavem et al., 2008). Prompt treatment is required to abort sustained seizure activity and to prevent recurrence of an attack (Smith, 2001; Alldredge et al., 2001).

A number of recent reviews have described consensus statements regarding pharmacologic treatment protocols for seizures (Pang and Hirsch, 2005; Ericksson and Kalviainen, 2005; Wolfe and Macfarlane, 2006; Meierkord et al., 2006; Prasad et al., 2007). Lorazepam and diazepam injection are considered the medications of first choice—–other benzodiazepines (midazolam) or other routes of delivery (rectal, buccal or intranasal (IN) are suitable alternatives. Interest has emerged in other delivery systems that enable rapid, non-injection-based delivery of seizure medications (Bhattacharyya et al., 2006; Mittal et al., 2006.). Transmembrane delivery of benzodiazepines has been described as very useful for emergency medical technicians in reducing time to drug administration and cessation of seizures in the pre-hospital setting, when actively seizing patients arrive in the emergency room, and at home when lay caregivers treat their dependents (Scheepers et al., 2000; Wilson et al., 2004; Harbord et al., 2004; Holsti et al., 2007).

Midazolam has been reported in case series and open-label, small subject sample and short duration clinical trials to be effective in treating seizures using the intravenous (IV), intramuscular, buccal and IN routes of administration (Chamberlain et al., 1997; McCormick et al., 1999; Scott et al., 1999; Jeannet et al., 1999; Towne and DeLorenzo, 1999; Appleton et al., 2004). The chemistry of midazolam permits a stable aqueous formula, with the only requirement that the solution be buffered to a pH < 4 for the drug to remain in solution. Once administered to a patient, the fraction of midazolam in the more permeant unionized state increases at physiologic pH of approximately 7.4. This phenomenon is conducive to rapid transit across membranes including the buccal and nasal mucosa and the blood—brain barrier.

Midazolam injection has been administered as nasal drops or sprays to patients having prolonged epileptic seizures, and status epilepticus (O'Regan et al., 1996; Fisgin et al., 2002; Lahat et al., 2000; Mahmoudian and Zadeh, 2004; Wilson et al., 2004). Dose selection for these trials appears to be derived from prior sedation/anesthesia studies and generally range from 0.2 to 0.3 mg/kg (Zedie et al., 1996). Importantly, the midazolam product delivered was a marketed dilute injection-based formulation, usually 5 mg/mL concentration. Several studies described drug administration using a disposable mucosal atomization device that is not currently approved by the FDA for this purpose (Wolfe and Macfarlane, 2006; Holsti et al., 2007). Other methods included standard syringes, pipettes or droppers as the administration device. The volume of injection sprayed/administered into the nares ranged from 1 to 4 mL, well beyond the volume a nasal cavity can retain and the common 100 μL per spray of most commercial over-the-counter and prescription nasal spray products (Costantino et al., 2007). In spite of only a few well-controlled clinical trials and a less than ideal ''product'' preparation, treatment outcomes (rapid seizure cessation) are described as being positive.

The aforementioned practice-based research trials administering midazolam injection from various devices to treat seizures speak clearly to an unmet medical need. A midazolam nasal spray formulation, using an appropriate IN administration device, and meeting current standards for nasal spray product design would be of great clinical utility. The present study was designed to demonstrate pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of two different doses of a novel midazolam nasal spray formulation compared to an IV injection in healthy volunteers.

2. Methods

2.1. Study design

This was an open-label, randomized, three-way crossover study design conducted at the University of Kentucky Hospital. On three different occasions, separated by a 1-week washout period, the subjects received in random order, counterbalanced so that an equal number of subjects received each treatment first, second, or third:

- *Treatment A*: 2.5 mg (5 mL of 1.0 mg/mL) IV midazolam infused over 15 min.
- *Treatment B*: 2.5 mg IN midazolam solution, one 2.5 mg/100 μL sprayer.
- *Treatment C*: 5.0 mg IN midazolam solution, two 2.5 mg/100 μL sprayers, one sprayer per naris.

The study was approved by the University of Kentucky Institutional Review Board prior to subjects being enrolled. The study was conducted according to International Conference on Harmonization (ICH) guidelines, Food and Drug Administration Good Clinical, Laboratory, and Manufacturing Practices, and the Declaration of Helsinki with written informed consent provided by all subjects.

The IV solutions were prepared for administration in the hospital pharmacy using commercially available midazolam (Versed® Injection by Hoffman-LaRoche). Midazolam (0.5 mL of 5.0 mg/mL) sterile solution was diluted to 10 mL with normal saline for a total volume of 10 mL to be infused over 15 min. A 25-mg/mL IN midazolam formulation was prepared under FDA Good Manufacturing Practices (GMP) conditions in the University of Kentucky College of Pharmacy Center for Pharmaceutical Science and Technology (CPST). The IN formulation contained midazolam 25 mg; polyethylene glycol 400, USP 0.18 mL; butylated hydroxytoluene, NF 0.10 mg; saccharin powder, NF 1.00 mg; propylene glycol, USP Q.S. to 1.00 mL. The aseptic formulation provided 2.5 mg of midazolam in 0.1 mL spray from a modified version of the commercially available, single-dose, metered sprayer (unit dose spray pumps, Pfeiffer of America, Princeton, NJ).

2.2. Subjects

Eighteen subjects, between 18 and 45 years of age, who were healthy volunteers within ±25% of ideal body weight in relation to height and elbow breadth and weighed at least 60 kg were enrolled. The subjects had no clinically significant previous nasal surgery or polyps or other physical abnormalities of the nose, abnormal vital signs, or cardiovascular, gastrointestinal, renal, hepatic, pulmonary, hematological or neurological disease. Subjects with a known history of Gilbert's Syndrome or with any other etiology for