The Journal of Emergency Medicine, Vol. 53, No. 3, pp. 397–404, 2017

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2017.05.029

Pharmacology in Emergency Medicine

EVALUATING CLINICAL EFFECTIVENESS AND PHARMACOKINETIC PROFILE OF ATOMIZED INTRANASAL MIDAZOLAM IN CHILDREN UNDERGOING LACERATION REPAIR

Sarah A. Mellion, MD,* David Bourne, PHD,† Lina Brou, MPH,* Alison Brent, MD,* Kathleen Adelgais, MD, MPH,* Jeffrey Galinkin, MD,‡ and Joseph Wathen, MD*

*Department of Pediatrics, Section of Emergency Medicine, University of Colorado School of Medicine, †University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Colorado, and ‡Department of Anesthesiology, Department of Pediatrics, University of Colorado, Anschutz Medical Campus, Aurora, Colorado

Corresponding Address: Sarah A. Mellion, MD, Department of Pediatrics, Section of Emergency Medicine, University of Colorado School of Medicine, Children's Hospital Colorado, 13123 East 16th Avenue, Box B251, Aurora, CO 80045

☐ **Abstract—Background: Atomized intranasal midazolam is a common adjunct in pediatrics for procedural anxiolysis. There are no previous studies of validated anxiety scores with pharmacokinetic data to support optimal procedure timing. Objectives: We describe the clinical and pharmacokinetic profile of atomized intranasal midazolam in children presenting for laceration repair. Methods: Children 11 months to 7 years of age and weighing <26 kg received 0.4 mg/kg of atomized intranasal midazolam for simple laceration repair. Blood samples were obtained at 3 time points in each patient, and the data were fit with a 1-compartment model. Patient anxiety was rated with the Observational Scale of Behavioral Distress. Secondary outcomes included use of adjunctive medications, successful completion of procedure, and adverse events. Results: Sixty-two subjects were enrolled, with a mean age of 3.3 years. The median time to peak midazolam concentration was 10.1 min (interquartile range 9.7–10.8 min), and the median time to the procedure was 26 min (interquartile range 21–34 min). There was a trend in higher Observational Scale of Behavioral Distress scores during the procedure. We observed a total of 2 adverse events, 1 episode of vomiting (1.6%) and 1 paradoxical reaction (1.6%). Procedural completion was successful in 97% of patients. Conclusions: Atomized intranasal midazolam is a safe and effective anxiolytic to facilitate laceration repair. The plasma concentration was >90% of the maximum from 5 to 17 min, suggesting this as an ideal procedural timeframe after intranasal midazolam administration.** © **2017 Elsevier Inc. All rights reserved.**

☐ **Keywords—anxiolysis; intranasal midazolam; laceration repair; pharmacokinetic**

INTRODUCTION

Intranasal midazolam (INM) is frequently used in the pediatric population to provide procedural anxiolysis (1–4). Intranasal administration avoids intravenous placement, results in rapid onset of effect, and increases bioavailability by circumventing first-pass metabolism (5–7). INM can be administered by intranasal drop instillation or with a mucosal atomizer device (MAD). Yealy et al. demonstrated adequate sedation in 73% of children with INM

Presented as a poster at the Pediatric Academic Societies Meeting, Emergency Medicine: Pain and Sedation, Baltimore, Maryland, May 2, 2016.

Reprints are not available from the authors.

RECEIVED: 8 December 2016; FINAL SUBMISSION RECEIVED: 8 May 2017;
ACCEPTED: 30 May 2017

drop administration; however, intranasal drop administration increases drug loss into the oropharynx, resulting in decreased absorption (4). The mucosal atomizer device (MAD Nasal; Wolfe-Tory Medical, Inc, Salt Lake City, UT) augments the delivery method of intranasal medications (2,8,9). Ljung et al. reported statistically better cooperation with procedures after spray INM compared to drop instillation (10). Lane and Schunk demonstrated that atomized INM for procedural anxiolysis exhibited adequate sedation for 94.6% of patients with a median dose of 0.4 mg/kg (2). Dosing of INM varies between studies, with multiple studies demonstrating equal safety with improved anxiolysis of 0.4 mg/kg when compared to lower doses (2,4,11,12). Pediatric INM pharmacokinetic studies are limited to premedication via nasal drop instillation for deep sedation in which a Tmax has been reported at 10 to 12 minutes (min) (13,14). No pediatric pharmacokinetic data exists for INM via a mucosal atomizer device.

Importance

There are no previous studies of validated anxiety scores and pharmacokinetic data in atomized INM. Adequate sedation has been reported with INM beginning 5 to 20 min after administration; however, there is little pharmacokinetic data available to support optimal procedure timing (4,6,15,16). Understanding the pharmacokinetic profile and clinical effects of atomized INM in children will provide the clinician with the ideal time window to perform a procedure. The MAD may promote more rapid absorption than drop instillation, which would be reflected in both clinical and pharmacokinetic parameters.

Goal of This Investigation

The goal of this investigation is to evaluate the serum concentration and clinical effects of INM administered via the MAD in a population of pediatric patients undergoing uncomplicated laceration repair.

METHODS

Study Design and Setting

This was a prospective study of a convenience sample of patients at a pediatric tertiary care facility with an emergency department that treats >70,000 children annually. Research assistants (RAs) trained in the study procedures provide coverage in the emergency department for 17 hours a day and screened patients for eligibility. Child life providers were present for 8 hours a day during the study, and were involved when available.

This study measured behavioral response levels that had not been previously described, and was approved by our institutional review board with informed consent.

Table 1. Demographics

Demographics (N = 62)	n (%) or Mean (SD)
Mean age, years (SD)	3.3 (1.6)
Gender, n (%)	
Male	28 (45.2)
Female	34 (54.8)
Mean weight, kg (SD)	15.1 (3.8)
Race, n (%)	
White	35 (56.5)
Black	8 (12.9)
Hispanic	10 (16.1)
Other	2 (3.2)
≥2 races	7 (11.3)
Anesthetic use, n (%)	
Topical	52 (82.5)
Injectable	16 (25.4)
Laceration location, n (%)	
Face	54 (85.7)
Upper extremity	6 (9.5)
Lower extremity	2 (3.2)
Child life provider, n (%)	14 (22.2)
Provider level of training, n (%)	
Attending	15 (24.2)
Fellow	13 (21)
Resident	25 (40.3)
PA/NP	9 (14.5)
ASA class, n (%)	
1	58 (93.5)
2	4 (6.5)

ASA = American Society of Anesthesiologists; NP = nurse practitioner; PA = physician assistant; SD = standard deviation.

Selection of Participants

Between September 2013 and November 2014, trained RAs approached children 1 month to 13 years of age after provider decision to administer INM for simple laceration repair, defined as laceration <2.5 cm in length. Patients older than 7 years of age provided assent. We enrolled English-speaking patients because the validated distress scale is only available in English. Patients received topical or injectable local anesthetic per provider preference. A standardized dose of 0.4 mg/kg midazolam 5 mg/mL divided between nares was administered via the MAD, with a maximum dose of 10 mg, which calculated to a maximum eligible