Pharmacokinetics and Tolerability of Nasal Versus Intravenous Midazolam in Healthy Dutch Volunteers: A Single-Dose, Randomized-Sequence, Open-Label, 2-Period Crossover Pilot Study

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ABSTRACT

Background: Intranasal (IN) midazolam is a potential alternative to rectal diazepam for the acute treatment of epileptic seizures.

Objective: The purpose of this pilot study was to investigate the pharmacokinetics and tolerability of IN midazolam (50 mg/mL) compared with intravenous (IV) midazolam (2.5 mg) in healthy adult volunteers.

Methods: In this single-dose, randomized-sequence, open-label, 2-period crossover pilot study subjects were randomly assigned to receive IN or IV midazolam, with a washout period of at least 5 days between treatments. The 50-mg/mL IN midazolam formulation consisted of 5 mg midazolam base per 0.1 mL (1 spray) and was administered once in 1 nostril. The IV midazolam solution (2.5 mg) was infused over 10 seconds. Blood samples were taken before and at regular intervals up to 240 minutes after dosing. Pharmacokinetic data (ie, C_{max}, T_{max}, $t_{½}$, and AUC) were analyzed using a 2-compartment model.

Results: Of 9 volunteers screened and enrolled, 7 completed the study (mean age 34.1 [9.0] years; mean weight, 68.6 [10.4] kg, range 53–89 kg; 6 men, 3 women; all white). The mean C_{max} of 78 (40) ng/mL was reached 44 minutes after IN administration, whereas the mean C_{max} was 51 (5) ng/mL after IV administration. The mean estimated $C_{t=5\ min}$ was 31.4 (28.1) ng/mL after IN administration. The elimination $t_{½}$ was 1.9 (0.41) hours for IN midazolam and 2.3 (0.19) hours for IV midazolam. The bioavailability of IN midazolam was 82%. There were few adverse events, with a local burning feeling in the nose being the most reported event (6 of 7 subjects).

Conclusions: In this select group of healthy volunteers, concentrations of midazolam >30 ng/mL were reached within 5 minutes of IN administration at a dose of 5 mg/0.1 mL. A burning feeling in the nostril was the main adverse effect. Additional research is needed to evaluate the safety profile, convenience, satisfaction, and efficacy of nasal midazolam in the treatment of adults with seizures. This trial is registered at www.isrctn.org, No. ISRCTN79059168. (*Clin Ther.* 2011;33:2022–2028)

Key words: intranasal, midazolam, pharmacokinetics, pilot study.

INTRODUCTION

Epilepsy is characterized by acute episodes of seizures that can last 5 minutes or longer or develop into status epilepticus. Seizures can cause brain damage as a result of metabolic abnormalities and can lead to significant morbidity and mortality.[1] Drugs with a rapid onset of action are needed to control acute and/or continuing seizures. In

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The Netherlands, rectal diazepam is currently used for this purpose. Although rectal diazepam is effective,[2] it also has several disadvantages. Namely, it has a long half-life (20–40 hours), which may result in prolonged sedation;[3] it is difficult to self-administer during an epileptic seizure; and its use can be socially embarrassing to both patients and bystanders.

A possible alternative rescue medication for acute treatment of epileptic seizures is midazolam, which is water soluble and can be administered by noninvasive routes, such as intranasally or buccally.[2,4] Intranasal (IN) midazolam might be a suitable mode of treatment because of its rapid onset of action,[5–7] relatively short duration of action, and noninvasive route of administration. Moreover IN delivery may improve the pharmacokinetic profile compared with other noninvasive routes of administration, such as oral or rectal administration.[8] Drugs are absorbed via the rich vasculature and numerous microvilli in the nasal cavity,[4,9–12] thereby avoiding first-pass hepatic elimination, which can influence the rate and extent of absorption. IN midazolam can be administered by patients when they are able or by bystanders, has a rapid onset of action, and has no significant effect on respiration and oxygen saturation.[13] However, many patients, especially children, experience IN administration of midazolam as painful, possibly because of the low pH (ie, 3.5) of the formulation[14–16] and the large volume (>0.15 mL) that needs to be administered to achieve a therapeutic concentration in systemic circulation. The maximum single spray volume per nostril is 0.15 mL (larger volumes may lead to irritation and run-off into the pharynx, which can lead to first-pass effects),[13] and the dose is based on a patient's body weight, with adults weighing <50 kg receiving 5 mg and heavier adults 10 mg.[12]

Several studies have investigated IN midazolam in healthy volunteers.[6,7,14,15,17–22] Four studies investigated the pharmacokinetics of the most concentrated nasal sprays available at the time of study initiation (25–30 mg/mL midazolam).[6,7,20,21] A spray volume of 0.167 to 0.200 mL per nostril in two divided doses would be needed to achieve the dose of 10 mg required for heavier adults. This large volume could lead to spillage and potentially altered pharmacokinetics.[23,24] The purpose of our pilot study was to investigate the pharmacokinetic parameters and tolerability of a more concentrated 50 mg/mL formulation compared with 2.5 mg intravenous (IV) midazolam in healthy adult volunteers.

MATERIALS AND METHODS

Participants

Healthy nonsmoking men and healthy, nonpregnant, nonsmoking women were considered eligible for inclusion in the study if they were aged ≥18 years and if they met American Society of Anesthesiology patient classification status I or II (ie, healthy or with mild systemic disease but no functional limitations). Potential participants were excluded if they had a runny nose or were allergic to benzodiazepines. The use of benzodiazepines and grapefruit juice was prohibited for a week before the intervention.

Study Design

Our randomized, nonblinded crossover study was performed at the Maastricht University Medical Centre, Maastricht, The Netherlands. Both treatments were administered by the study nurse (MT), with a washout period of at least 5 days between treatments. The newly developed IN midazolam formulation consisted of 5 mg midazolam base per 0.1 mL (1 spray) and was administered once in 1 nostril. The IV midazolam dose (2.5 mg administered over 10 seconds) was chosen to avoid side effects. The study nurse (MT) administered IN midazolam with the subject sitting upright; IV midazolam was administered with the subject lying down. Subjects fasted overnight and were not allowed to eat 4 hours after study drug administration.

The study protocol was approved by the Medical Ethics Committee of Maastricht University Medical Centre and written informed consent was obtained from all participants before enrolment.

Study Drugs

Study medications were developed and prepared by the Department of Clinical Pharmacology and Toxicology at Maastricht University Medical Centre. The midazolam nasal spray consisted of 556.2 mg midazolam hydrochloride, 8 mL propylene glycol, and 2 mL water for injection; midazolam was administered in a single spray of 0.1 mL. The spray device came from Pfeiffer (Radolfzell, Germany). The IV injection consisted of a single 2.5-mg midazolam dose administered over 10 seconds; the cannula was flushed with 4 mL saline.

Tolerability Assessments

Participants were asked to report any untoward effects experienced during the study, including both local