Intranasal Midazolam for Treatment of Seizures in Children in the Emergency Setting

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Abstract

Seizures in children are a frightening experience for families and care providers. Because the duration of seizure activity impacts on morbidity and mortality, effective methods for seizure control should be instituted as soon as possible, preferably before arrival at the hospital. Since parental methods of drug delivery are not available to most caregivers, and rectal diazepam, the most common home therapy, is expensive and often ineffective, new routes of administration are needed.

This review examines recent research suggesting that intranasal administration of midazolam is at least as effective as the intravenous route for seizure cessation. Intranasal administration delivers the drug directly to the blood and cerebrospinal fluid via the nasal mucosa. It has been found to be safe, effective, and easy to use by parents and paramedics.

MeSH Words: Seizures, Midazolam, Benzodiazepines, Children

Introduction

Seizures are common in the pediatric population. The cumulative lifetime incidence of epilepsy is 3%, with onset during childhood in more than half the cases [1]. Current evidence suggests that prolonged seizures are best stopped with early treatment [2]. In the hospital, benzodiazepines are currently the first line of therapy, although intramuscular paraldehyde is used in many parts of the world when immediate intravenous access is unavailable [2, 3]. Outside the hospital, where intravenous and intramuscular therapy may be difficult or impossible to administer, rectal diazepam has emerged as the primary treatment option for breakthrough seizures [4]. However, rectal diazepam has a slower onset of action than the intravenously delivered drug and is not as effective at controlling seizures [4]. Other disadvantages include the lower social acceptability of the rectal route [5] and the high cost of the commercially available drug compared to the generic formulations of other commonly used benzodiazepines [4].

The oral transmucosal route offers a potential alternative means of delivery of benzodiazepine treatment. However, buccal administration has been found to provoke gagging, coughing and aspiration, and is more amenable to a small volume of drugs, and sublingual delivery is difficult to use when the teeth are clenched during a tonic-clonic seizure [4]. The present review describes recent findings for the

effectiveness and safety of intranasal transmucosal delivery of midazolam in the control of acute seizures in children.

Intranasal Administration of Midazolam

Ayurveda, the "science of life", has been practiced in India for thousands of years. It is based on the notion of restoring the balance and harmony of the individual by changes in daily living in order to promote health. Ayurvedic practitioners believe that "the nose is the door to the brain" and that treatment with nasal drops (nasya) improves voice, vision, and mental clarity [6].

The nasal mucosa provides a large (180 cm^2), highly vascular absorptive surface adjacent to the brain. Together with the neighboring olfactory mucosa, it offers a direct pathway for drug absorption into the bloodstream and cerebrospinal fluid. Therefore, the nasal route is a good option for drugs that undergo extensive first-pass hepatic metabolism, increasing their bioavailability, and drugs with erratic absorption patterns. It is also advantageous when drugs with a short latency of action -- such as benzodiazepines -- are required [7].

The intranasal administration of midazolam for the treatment of seizures has been found to be safe and efficacious in numerous clinical studies, in the hospital, before arrival at the hospital, and in extended care and home settings [4,5,8-12]. Midazolam is a water-soluble, hydrophilic compound, prepared at a pH of 3.5 and therefore reliably absorbed intramuscularly. At physiological pH, the ring structure of the molecule closes, making it highly lipophilic. As a result, it crosses the blood-brain barrier and enters the central nervous system, with a rapid clinical effect. The elimination half-life of midazolam is usually between 1.5 and 3.5 hours, and is similar for the nasal route, at a dose of 0.2 mg/kg, and the intravenous route [9]. . Serum levels of intranasal midazolam have been shown to be comparable with serum levels of injected midazolam within 10 minutes of delivery [4].

When employing the intranasal route for benzodiazepines, it is important that the drug be highly concentrated and that it be delivered directly to the surface of the mucosa. Too large an amount or too-rapid administration may result in suboptimal absorption and loss of drug into the pharynx, rendering it ineffective. The volume limit is about 0.5 ml per nostril [10]. Placing half the medication into each nostril will reduce the volume per nostril while doubling the available surface area for absorption [11]. .

Although the presence of an upper respiratory tract infection may help drug absorption by increasing blood flow to the nasal mucous membrane, nasal secretions can theoretically dilute the midazolam solution and interfere with its contact with the absorbing surface [9]. In one randomized controlled trial, most of the 21 children included had an upper respiratory tract infection, but only 3 showed ineffective absorption of midazolam and subsequent poor seizure control [9]. In another study of 11 children with nasal congestion, all responded to their allocated treatment within 10 minutes [3].

Efficacy of Transmucosal Midazolam

Three randomized controlled trials of the transmucosal administration of midazolam (buccal or nasal) found it to be effective in interrupting seizures and preferable to rectal diazepam because of ease of use and social acceptability [12-14]. Scott et al [12], in a study of epileptic students attending an extended-care school, found that oral transmucosal midazolam stopped seizures in 30/40 children whereas rectal diazepam did so in 23/39 ($p=0.16$). Although these differences did not achieve statistical significance, the trend toward a better outcome with oral delivery along with its greater social acceptance led the school to switch to the oral transmucosal route. Camfield et al [13], using the same design, found a similar efficacy and drew identical conclusions. In the third study, Fisgin et al. [14] compared intranasal midazolam to rectal diazepam. Midazolam aborted 20/23 seizures and rectal diazepam, 13/20 ($p<0.05$). Together, these findings indicate that compared to rectal diazepam, transmucosal midazolam is more convenient, easier to use, and more socially acceptable; when given via the intranasal route, it is also more effective.

Intranasal midazolam was also found to be a good option for home administration by parents. Wilson et al [15] noted that 33 of 40 parents questioned reported intranasal midazolam to be effective, and 83% preferred it to rectal diazepam.

Effectiveness of Intranasal versus Intravenous Benzodiazepines

Lahat et al. [9] randomized 52 children with prolonged seizures (10 minutes or more) to receive intravenous diazepam, 0.3mg/kg IV, or intranasal midazolam, 0.2 mg/kg. Equally good control was achieved in both groups (23 and 24 patients, respectively), but the mean time from patient arrival to seizure cessation was significantly shorter in the patients receiving midazolam (6 minutes vs. 8 minutes, $p<0.001$). The authors assumed the more rapid effect in the intranasal group was attributable to the time saved by eliminating the need to insert an intravenous line. A similar study by Mahmoudian and Zadeh [16], with a slight change in dosages, concluded that both methods were equally effective. These studies agree with the survey of Wilson et al. [15], indicating that transmucosal midazolam may be used not only in medical centers, but also in general practitioners' offices as well as at home by parents and families of seizure-prone children, after appropriate instruction.

Safety of Intranasal Midazolam

Midazolam given intranasally has been shown to be safe for children undergoing various diagnostic studies and minor surgical procedures [17]. Several clinical studies reported similar result s in adults and children with epilepsy [18]. The intranasal route appears to be equally safe to the intravenous and intramuscular routes, which have not been found to be associated with respiratory changes. There were reports of their association with hypertension, bradycardia, and hypoxia in adults and children, but these changes were always mild and transient, and no patient required intubation or mechanical ventilation [19]. In a hospital-based randomized controlled study of children treated for acute seizures by rectal diazepam or buccal midazolam, the incidence of respiratory depression was similar for both groups [20], and the overall rate (5.5%) was lower than reported in an earlier study of diazepam (rectal or intravenous) [21].

Lahat et al [22] administered intranasal midazolam to 20 children aged 6 months to 5 years with acute seizures. In 19, control was achieved within 3.5 minutes of drug administration, and none of the children had clinical signs of respiratory distress or bradycardia. Accordingly, the randomized controlled trials of Scott et al. [12] and Fisgen et al. [14] also reported no adverse cardiorespiratory effects in either the study or control groups. These findings have important implications, as the specific emergency treatment used may be one of the many factors responsible for respiratory depression.

Other Intranasal Benzodiazepines

In a randomized controlled trial comparing intranasal lorazepam 100 μg/kg to intramuscular paraldehyde 0.2 mL/kg in 160 children (age 2 months-12 years) with prolonged clonic tonic seizures, no significant between-group difference was found in the rate of seizure cessation at 10 minutes after drug delivery (lorazepam 75%, paraldehyde 61%, $p=0.06$) [3]. The lorazepam in this study was administered via mucosal atomization (using an aerosolized device), which distributes the particles better than dripping with a syringe and targets a larger surface area of olfactory ephithelium. As a result, the maximum plasma concentration of lorazepam increased from about 50% to 80% of the plasma concentration reached by the intravenously administered drug. Besides the improved bioavailability, aerolization eliminated concerns related to nasal congestion [3].

Summary

Intranasal midazolam is safe and effective for treating seizures in the hospital, before arrival at the hospital, and in outpatient settings. Compared with the current standard of care using rectal diazepam, intranasal midazolam is more efficacious and easier to use, has a shorter postictal period, and is more socially acceptable. Together, these advantages make intranasal midazolam a viable alternative to rectal diazepam as the preferred method for treatment of seizures in patients without an intravenous access. The rapid onset of action of intranasal midazolam is noteworthy, given that early treatment can reduce the morbidity and mortality of prolonged status epilepticus. Treatment should preferably start before arrival to the hospital, but only by trained health-care personnel or families.

We speculate that in the acute setting, since several benzodiazepines via various delivery routes have been found effective, perhaps researchers should broaden the one-drug/one-

route approach to a range of interventional options in order to better tailor treatment to the individual patient.

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