Intranasal midazolam for seizure cessation in the community setting

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Abstract

Question  There are times when parents arrive to my clinic after their child has had a seizure and a second seizure takes place in the clinic. While waiting for transport to the hospital, are there ways to stop the seizures without the need to obtain intravenous access in the clinic?

Answer  Intravenous diazepam has been a first-line therapy to stop seizures in children for many years. Other routes of drug administration such as intramuscular, rectal, and buccal are available but have several limitations. More evidence suggests that the intranasal route to administer drugs is quick and effective in children, and the use of midazolam has been continuing to show promise in seizure cessation. With its good safety profile, intranasal midazolam can be used in the clinic and prehospital setting for seizure cessation in children.

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Ten percent of children will experience seizures during childhood, most of them lasting less than 5 minutes.1 Longer seizures require prompt cessation; the sooner a seizure is treated, the more likely it will be controlled.2 When seizures are prolonged or seizure activity is recurrent (status epilepticus), patients are at risk of neurologic complications including intractable mesial temporal lobe epilepsy—a severe condition associated with increased morbidity and poor psychosocial outcome,3 developmental delay, and hemiplegia, as well as increased mortality.4 Prehospital intervention is frequently needed to shorten seizure duration.5

Benzodiazepines are the first-line agents to stop seizures.6 They allosterically modify \( \gamma \)-aminobutyric acid (GABA) receptors located in neuron synapses in the central nervous system (CNS). This modification enhances GABA receptors’ response to GABA, thus making neurons resistant to excitation.5 Rapid penetration of benzodiazepines into the CNS is critical for efficacy and is determined by the agent’s chemical properties (polarity and molecular weight).6

Route of administration

Diazepam (a benzodiazepine) is usually given intravenously or rectally, as its absorption is slow if given intramuscularly.7 However, it has a short duration of action and tends to accumulate after repeated doses, with the possible rare complication of brainstem depression leading to bradypnea or respiratory arrest.8 Rectal administration does not necessitate venous access but has variable and unpredictable drug absorption, induces hepatic first-pass metabolism, and triggers social awkwardness for patients and providers.6 Buccal administration has been found to provoke gagging, coughing, and aspiration, and is more amenable to a small volume of drugs.9 Sublingual delivery is difficult to use during a seizure.9

Intranasal drug administration on the other hand is painless, does not require intravenous access, and is a route easily accessible for all patients. The nasal cavity is covered with a thin mucus layer and a monolayer ciliated epithelium, and is innervated by an abundant underlying blood supply, permitting drugs to rapidly and predictably bioavailable.5 This route of administration allows transfer of molecules from the olfactory bulb to the brain, bypassing the blood-brain barrier, resulting in easier penetration of drugs into the CNS.11

Medications suitable for intranasal use must be water soluble, small enough to permeate the nasal mucosa, and potent enough to be effective in small doses.12 In addition to the pharmacologic advantages, the convenience of intranasal administration and its social acceptability might make intranasal midazolam the preferred treatment for seizures in prehospital and hospital settings.6

Intranasal midazolam

Midazolam, the first water-soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and...
Midazolam can be given intravenously, intramuscularly, buccally, and rectally, as well as via the nasal mucosa. It is water soluble but becomes lipid soluble at physiologic pH levels, allowing it to cross the nasal mucosa into the CNS with a rapid onset of action. Midazolam has become a prevalent preanesthetic agent because of its rapid onset and relatively short duration of action making it less likely than diazepam to accumulate. Given intranasally as an anesthetic agent, midazolam has been shown to be safe and effective in children undergoing various diagnostic studies and minor surgical procedures such as computerized tomography, echocardiography, dental procedures, and suture laceration. The incidence of adverse effects is low; the most common adverse effects reported following the administration of intranasal midazolam are burning sensation or irritation in the nose lasting for 30 to 45 seconds and a bitter taste in the mouth.

**Seizure cessation**

*Effectiveness of intranasal midazolam versus intravenous diazepam.* Lahat et al randomized 53 children to either intranasal midazolam or intravenous diazepam and showed that once the drug was administered, control of seizures was faster with diazepam than with midazolam; however, the total time from arrival at hospital to cessation of seizures was shorter with midazolam (6.1 [SD 3.6] minutes vs 8.0 [SD 4.1] minutes; P < .01) because drug administration was faster in the midazolam group. Among 70 children randomized to either intranasal midazolam or intravenous diazepam, 19 time to seizure cessation was longer with intranasal midazolam compared with intravenous diazepam (3.58 [SD 1.68] minutes vs 2.94 [SD 2.62]; P = .007); however, intranasal midazolam was quicker to administer. Other randomized studies comparing intranasal midazolam and intravenous diazepam reported significantly shorter time to cessation of seizures with intranasal midazolam than with intravenous diazolam after arrival at hospital (5.25 [SD 0.86] minutes vs 6.51 [SD 1.06] minutes [P < .001] and 6.67 [SD 3.21] minutes vs 17.18 [SD 5.09] minutes [P < .001]) for intranasal midazolam and intravenous diazepam, respectively.

**Intranasal midazolam versus rectal diazepam.** In a study from 2006, mean time to seizure cessation in 46 children was 1.95 and 2.97 minutes for intranasal midazolam or rectal diazepam, respectively (P < .01).

Seizures stopped within 10 minutes of drug administration in 97% of patients in the midazolam group and 89% of patients in the diazepam group (P = .06). Fisgin et al evaluated 45 children and reported intranasal midazolam to be more likely to stop seizure activity within the first 10 minutes (87% [20 of 23 patients] vs 59% [13 of 22 patients]; P < .05). In addition, more patients required a second anticonvulsant to stop seizures if randomized to the rectal diazepam group. Holsti et al evaluated 92 seizure episodes where caretakers administered medications at home before calling emergency medical services. Those in the intranasal midazolam group reported a median time to seizure cessation of 3 minutes whereas those in the rectal diazepam group had a corresponding time of 4.3 minutes (P = .09).

**Device for nasal drug administration**

In traditional studies with intranasal midazolam, the drug was administered with a syringe, dripping midazolam in both nostrils. When employing the intranasal route for midazolam, it is important that the drug is delivered directly to the surface of the mucosa. Too large an amount or too rapid administration might result in suboptimal absorption and loss of drug into the pharynx, compromising its effectiveness.

A recent advancement is the use of an atomizer, allowing delivery directly to the surface of the mucosa and improved amount and pace of drug absorption. The atomizer is placed on top of a syringe that distributes midazolam in a 30-µm particle size, coating the nasal mucosa. Nasal spraying provides optimal mucosal distribution and slower spray clearance.

**Conclusion**

Intranasal midazolam is safe and effective for treatment of acute seizures in children and might be quicker than intravenous diazepam if stop seizures. Intranasal midazolam should be considered as a convenient anticonvulsant agent for community, prehospital, and emergency department use in children when intravenous access is not available.


