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Review

# Intranasal therapies for acute seizures

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ABSTRACT

Most seizure emergencies occur outside of the hospital, and there is a need for treatment interventions that can be administered quickly and safely by nonclinical caregivers. Intranasal benzodiazepine administration does not require intravenous access and offers rapid seizure cessation. Intranasal midazolam is faster at aborting seizure activity than rectal diazepam and quicker to administer than intravenous diazepam. Although time to seizure cessation varies from study to study, intranasal midazolam is efficacious when administered not only by emergency department personnel but also by paramedics and caregivers in out-of-hospital and home settings. Absorption of midazolam intranasal formulations appears to be relatively rapid compared to diazepam formulations. Its shorter elimination half-life may also be beneficial in that patients may more quickly return to normal function because of rapid offset of effect. On the other hand, the faster rate of elimination of midazolam may expose patients to a higher rate of seizure recurrence compared with diazepam. Two diazepam formulations and one midazolam formulation are being currently developed for intranasal use.

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## 1. Introduction

The spectrum of seizure emergencies covers situations from prolonged single seizures to acute repetitive seizures or seizure clusters [1] and further to status epilepticus (SE). Timely administration of rescue medication for prolonged seizures or seizure clusters is necessary to prevent progression to SE. Most seizure emergencies occur outside of the hospital, and there is a significant need for treatment interventions that can be administered quickly and safely by nonclinical caregivers at home, school, work, or any institution. With immediate recognition of prolonged seizures and seizure clustering and prompt medical treatment, the risk of morbidity and mortality related to SE can be reduced [2].

Rectal diazepam provided a much needed treatment option for out-of-hospital prolonged seizures and seizure clusters, but the route of administration may be problematic in social settings and fear of liability seems to be a critical issue for many schools and teachers [3]. Several alternative routes for acute administration of benzodiazepines are being explored. Buccal administration of midazolam for seizure clusters is widely used in many parts of the world [4] but carries risks of aspiration or inconsistent absorption due to ictal hypersalivation and buccal secretion [5,6]. Intranasal administration of benzodiazepines provides rapid absorption and levels comparable with rectal dosing [7] and is under active investigation. This review summarizes recent advances in intranasal treatment of prolonged seizures and seizure clusters.

## 2. Intranasal drug delivery

Intranasal drug administration is painless, does not require intravenous access, and is immediately available for all patients. The nasal cavity's rich vascular plexus permits topically administered drugs to rapidly achieve effective blood levels [8]. Direct absorption into the blood stream avoids gastrointestinal destruction and hepatic first-pass metabolism, allowing more drug to be rapidly and predictably bioavailable compared with oral administration.

Because the nasal mucosa is nearby the brain, cerebrospinal fluid drug concentrations can exceed plasma concentrations. This concept of transfer of molecules from the olfactory bulb to the brain is referred to as the nose–brain pathway and has implications when centrally acting medications such as antiseizure drugs are delivered nasally [9].

The larger the nasal mucosal surface area is covered, the more medication can be absorbed [10]. Seizure rescue medication needs to be delivered without active inhalation. Spray or atomized pump gives the best mucosal distribution. In addition, clearance of spray is much slower than clearance of drops since the spray deposits on nonciliated areas whereas nose drop solutions are primarily distributed on ciliated surfaces [10]. With drops, the head position is also crucial: if the patient fails to hold their head in the best position, much of the drug is either not delivered or lost to the external environment or into the throat. Nasal spraying of medications is far easier to employ as it can be

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delivered from any position, and because the medication is sprayed/atomized as a mist, less is likely to be blown back out the nose.

## 3. Midazolam

### 3.1. Bioavailability and pharmacokinetics

Midazolam is a lipid soluble benzodiazepine with rapid onset of action and short duration. The greater that a drug's lipid solubility (lipophilicity) at physiological pH is, the faster its absorption across membranes including nasal tissues as well as the blood–brain barrier. Nasally administered midazolam reaches peak concentrations ($T_{max}$) within 10 min, and its bioavailability ranges from 50% to 72% [11,12] (Table 1). The elimination half-life is short (3 h), but diseases like multiorgan failure may decrease the clearance [12].

USL261 is an investigational formulation of midazolam optimized for intranasal dosing and currently under development for the intranasal rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity (e.g., acute repetitive seizures and seizure clusters). The pharmacokinetics of USL261 has been studied in healthy volunteers, and these results have been compared with midazolam injection solution administered nasally and midazolam administered by intravenous infusion [13] (Table 1). USL261 provided rapid delivery of midazolam, with median $T_{max}$ values observed between 10 and 12 min and mean $T_{1/2}$ between 3.6 and 3.8 h. USL261 demonstrated an increased systemic exposure and improved bioavailability compared with intranasal midazolam injection.

### 3.2. Safety data from other indications

Intranasal midazolam use has been reported since 1988 [14] for procedural sedation in both children and adults. Use of intranasal midazolam (0.1–0.3 mg/kg) has been reported especially in children undergoing dental procedures, anesthesia induction, suture laceration, and pediatric imaging studies [12,15]. Sedation occurs rapidly, generally within 5–10 min, and lasts for 30–60 min.

The incidence of adverse effects is low. The most common adverse effects reported following intranasal midazolam are burning or irritation in the nose lasting for 30–45 s and a bitter taste in the mouth [12,15]. Other adverse effects are similar to those of benzodiazepines administered via other routes and primarily include cardiorespiratory depression.

### 3.3. Clinical studies in acute seizures

Intranasal midazolam has been reported since 2000 [16] for use in the treatment of acute seizures in both children and adults. Scheepers et al. [16] reported the first open, noncomparative study. A dose of intranasal midazolam (5 mg if the patient weighed less than 50 kg and 10 mg if the patient weighed over 50 kg) was prescribed for those who had previously responded to other rescue medications. Twenty-two patients received 84 treatment episodes, and 79 of these were considered clinically effective (94%).

Four studies have compared intranasal midazolam to rectal diazepam (Table 2) [17–20]. Bhattacharyya et al. [17] randomly assigned 46 children to receive treatment with rectal diazepam and intranasal midazolam with doses of 0.3 mg/kg body weight and 0.2 mg/kg body weight, respectively. Both febrile and afebrile seizures were included. Cessation of seizures was defined as visible stopping of the convulsions or a return of "purposeful response to external stimuli." Mean time to seizure cessation was 2.97 min and 1.95 min in the rectal diazepam and intranasal midazolam groups, respectively ($p < 0.01$). Seizures stopped within 10 min of drug administration in 89% of the diazepam group and 97% of the midazolam group ($p = 0.06$).

de Haan et al. [18] reported a study of 21 adult patients with medically refractory epilepsy in whom 124 seizure exacerbations were treated by their caregivers alternatively with 10 mg rectal diazepam and 10 mg intranasal midazolam two or three treatments with each medication for each patient. No difference in efficacy or time to effect between the two drugs was demonstrated. Common treatment emergent adverse effects were drowsiness for both drugs in more than 50% of the administrations and short-lasting local irritation for intranasal midazolam in 29% of administrations. No severe adverse events occurred. The nasal spray was preferred over the rectal solution by 16 of 21 caregivers and patients conjointly.

Fişgin et al. [19] evaluated 45 children who presented to the emergency room with an acute seizure and were randomized to rectal diazepam or intranasal midazolam. Both afebrile and febrile seizures were included. Seizure cessation within 10 min occurred in 60% ($n = 13$) of those receiving rectal diazepam versus 87% ($n = 20$) of patients administered intranasal midazolam ($p < 0.05$). The authors concluded that intranasal midazolam is a more effective anticonvulsant than rectal diazepam.

Holsti et al. [20] evaluated 92 seizure episodes where caretakers administered medications at home prior to calling emergency medical personnel. Caretakers were randomized to use either intranasal midazolam 0.2 mg/kg (maximum, 10 mg) or rectal diazepam 0.3 to 0.5 mg/kg (maximum, 20 mg) and were instructed to administer the drug if the patient's seizure lasted more than 5 min. There were 50 children who received intranasal midazolam and 42 who received rectal diazepam. The intranasal midazolam group reported a median time to seizure cessation of 3 min whereas the rectal diazepam group had a corresponding time of 4.3 min ($p = 0.09$).

Four studies have compared intranasal midazolam (0.2 mg/kg) to intravenous diazepam (0.3 mg/kg) (Table 2) [21–24]. In the study by Lahat et al. [21], control of seizures in children with febrile seizures was faster with intravenous diazepam than with intranasal midazolam, but the time to cessation of seizures after the arrival of a child at the hospital was faster with intranasal midazolam (6.1 +/− 3.6 min vs 8.0 +/− 4.1 min, $p < 0.01$). Mahmoudian and Zadeh [22] found that the interval between treatment and seizure termination was longer with those treated with nasal midazolam compared to those given intravenous diazepam, but intranasal midazolam was quicker to administer. Mittal et al. [23] randomized 76 patients, and the mean time to control seizures after arrival in the hospital was significantly shorter in the midazolam group compared to the diazepam group (5.25 +/− 0.86 min vs 6.51 +/− 1.06 min, $p < 0.001$). Thakker and Shanbag [24] randomized 50 children aged from 1 month to 12 years presenting with acute seizures. The mean interval between cessation of seizures and arrival at the hospital was significantly shorter in the midazolam group [6.67 min (SD: 3.12)] compared to the diazepam group [17.18 min (SD: 5.09)]. No significant side effects were observed in either group.

Although upper respiratory tract infection might help absorption by increasing blood flow to the nasal mucous membrane, the presence of nasal secretions could dilute the midazolam solution and interfere with its contact with the absorbing surface [21]. In the study by Lahat and colleagues, most of the 26 children treated with intranasal midazolam had an upper respiratory tract infection, and this only affected the absorption of midazolam and subsequent seizure control in three episodes. Across the eight intranasal midazolam studies, the incidences of respiratory events requiring intubation (1.0%) and of need for supplemental oxygen (4%) were low.

## 4. Diazepam

Diazepam has a substantially longer elimination half-life (about 50 h) than midazolam, which may provide a greater duration of effect. Several intranasal diazepam formulations have been developed. Absorption following intranasal administration of diazepam appears to be somewhat faster ($T_{max}$ below 1 h) than the rectal route based on $T_{max}$ (Table 1). High bioavailability rates of the latest intranasal formulations, DZP-b compared with the intravenous formulation (97%) [25] and DZP-c with the rectal formulation (89%) [26], have been described.

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