The Nose Knows: Intranasal Midazolam To Treat Acute Seizures During Inpatient Epilepsy Monitoring

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Efficacy, Tolerability, and Safety of Concentrated Intranasal Midazolam Spray as Emergency Medication in Epilepsy Patients During Video-EEG Monitoring

von Blomberg A, Kay L, Knake S, Fuest S, Zöllner JP, Reif PS, Herrmann E, Balaban Ü, Schubert-Bast S, Rosenow F, Strzelczyk A. *CNS Drugs.* 2020;34(5):545-553. doi: 10.1007/s40263-020-00720-w

Background: An efficient, well tolerated, and safe emergency treatment with a rapid onset of action is needed to prevent seizure clusters and to terminate prolonged seizures and status epilepticus. Objectives: This study aimed to examine the efficacy, tolerability, and safety of intranasal midazolam (in-MDZ) spray in clinical practice. Methods: In this retrospective, multicenter observational study, we evaluated all patients with peri-ictal application of in-MDZ during video-electroencephalography (EEG) monitoring at the epilepsy centers in Frankfurt and Marburg between 2 014 and 2017. For every patient, we analyzed the recurrence of any seizure or generalized tonic-clonic seizures after index seizures with and without in-MDZ administration. Treatment-emergent adverse events were also evaluated. Results: Intranasal MDZ was used in 243 patients with epilepsy (mean age 35.5 years; range 5-76 years; 46.5% female) for treatment of 459 seizures. A median dose of in-MDZ 5 mg (ie, 2 puffs; range 2.5-15 mg) was administered within a median time from EEG seizure onset until in-MDZ application of 1.18 minutes (interquartile range [IQR] 1.27), while median time from clinical seizure onset until in-MDZ administration was 1.08 minutes (IQR 1.19). Intranasal MDZ was given within 1 minute after EEG seizure onset in 171 seizures. An intraindividual comparison of seizures with and without application of in-MDZ was feasible in 171 patients, demonstrating that in-MDZ reduced the occurrence of any (Cox proportional-hazard model $P < .001$) and generalized tonic-clonic seizure (Cox proportional-hazard model $P = .0167$) over a period of 24 hours. The seizure-free time span was doubled from a median of 5.0 hours in controls to a median of 10.67 hours after in-MDZ administration. We additionally clustered in-MDZ administrations for the 119 patients who received in-MDZ more than once, comparing them with the index cases without in-MDZ. Even when considering subsequent seizures with in-MDZ administration, a patient receiving in-MDZ is still half as likely to incur another seizure in the upcoming 24 hours as compared with when the same patient does not receive in-MDZ (hazard ratio 0.50; 95% CI: 0.42-0.60; $P < .01$). Intranasal MDZ was well tolerated without major adverse events. The most common side effects were irritation of the nasal mucosa (37 cases [8.1%]), prolonged sedation (26 cases [5.7%]), and nausea and vomiting (12 cases [2.6%]). A decline in oxygen saturation was measured after 78 seizures (17%). Conclusion: We conclude that in-MDZ is a safe and efficient treatment option to prevent short-term recurrence of seizures. Intranasal MDZ can be administered very quickly by trained staff within 1 to 2 minutes after seizure onset. No major cardiocirculatory or respiratory adverse events were observed.

Commentary

The first alternative to oral or intravenous "rescue" treatments for acute repetitive seizures (clusters) became available in the United States when rectal diazepam gel was approved in 1997.[1] It was shown in 2 randomized placebo-controlled trials to be effective at reducing subsequent seizures, to produce meaningful plasma concentrations as soon as 15 minutes after dosing, to be generally safe, to be well tolerated, and to produce maximum plasma concentration (Tmax) at 90 minutes. It has been used extensively by parents and caregivers of young children,

but for older children and adults the rectal route was not desirable owing to embarrassment or difficulty administering the medication.

Over the ensuing 2 decades, numerous formulations of benzodiazepines, chiefly diazepam and midazolam (MDZ), were studied using buccal, intranasal, intramuscular, and inhaled routes of administration. These were used off-label in the United States particularly by parents or caregivers during clusters in persons with epilepsy to prevent progression to status epilepticus. One method used was to open an ampule of the

injection form of MDZ, draw 1 mL into a syringe, attach an atomizing device, and spray the liquid into the nostril of the patient.[2] This large volume of liquid can dribble out of the nose or can be swallowed leading to gastrointestinal delivery with a delayed Tmax and with resultant first pass metabolism. Buccal MDZ is approved in some European countries, but postictal hypersalivation, jaw clenching, and possible aspiration are problematic.

In the highlighted article, von Blomberg et al[3] report a retrospective study of 243 children and adults aged 5 to 76 (mean 35.5) years who had a total of 459 seizures. They describe the use of intranasal midazolam (in-MDZ) to abort seizures and control seizure frequency during inpatient video-electroencephalography monitoring (VEEG). This medication was compounded by pharmacists at each of 2 German university hospitals and contained 2.5 mg per spray. Patients had received a median dose of 5 mg (range 2.5-15 mg). Following an index seizure, the occurrence of tonic-clonic convulsions treated with in-MDZ was compared to an untreated group. In-MDZ was given quickly: within 1.08 minutes of clinical onset. Of the total 243 patients, 171 had seizures both treated with and not treated with in-MDZ which allowed for a comparison of the results of treatment and nontreatment within the same patient. Of these 171 patients, 119 received in-MDZ following more than 1 seizure. The remaining 72 patients had received in-MDZ treatment with every seizure during VEEG, so their responses were only used to add to the safety and tolerability results.

Intranasal MDZ significantly reduced the occurrence of both any seizure and a tonic-clonic convulsion over the subsequent 24 hours, and it increased the seizure-free time span from a median of 5.0 to 10.67 hours. Of the total cohort, 93.6% of patients remained seizure-free for 1 hour with in-MDZ (compared to 85.4% without in-MDZ), and 29.2% were seizure-free for 24 hours with in-MDZ (compared to 14% without drug). Among the 119 patients who received repeated in-MDZ treatment, there was no loss of this effect at delaying subsequent seizures. Adverse events included nasal mucosa irritation in 8.1%, prolonged sedation in 5.7%, and nausea and vomiting in 2.6%. A decrease in blood oxygen saturation <90% was noted with 17% of seizures. No major cardiovascular or pulmonary adverse events were observed.

Within the limitations of a retrospective design, this inpatient study supports the effectiveness, duration of effect, and low percentage of prolonged sedation. Effectiveness is supported by the finding of a delay not only of tonic-clonic convulsions but also of all seizure types. Furthermore, no acute tachyphylaxis was seen among patients who received treatment for a sequence of seizures.

A strength of the study's methodology is that the volume of the 2.5 mg of MDZ was only 0.14 mL as described in their earlier report.[4] This is an important advantage over the off-label use described above in which 1 mL of liquid is sprayed into the nose. A limitation of the study is its retrospective design. Therefore, randomization and blinding were impossible, and multiple possible adverse effects and blood oxygen saturation and respiratory rate measurements were not prespecified and systematically assessed.

In contrast, a study by Detyniecki et al[5] was a randomized, double-blind, placebo-controlled trial of in-MDZ in patients at least 12 years of age conducted in an outpatient setting (where most seizure clusters occur). Patients were taking their usual anti-seizure medications (ASMs), and seizure reporting was by caregivers. Exclusion criteria were an oxygen saturation <90% for > 30 seconds or excessive sedation after and in-clinic test dose of 10 mg of in-MDZ or a history of severe cardiopulmonary disease or acute narrow-angle glaucoma. Patients received a blinded dose of in-MDZ 5 mg or placebo during a seizure cluster. Subsequently, all patients were eligible to receive an optional, open-label 5-mg MDZ dose within 10 minutes. Treatment success (defined as seizure termination within 10 minutes of, and no recurrence within 10 minutes to 6 hours after, receiving study drug) occurred in 53.7% of MDZ and 34.3% of placebo treated patients ($P = .0069$). The proportion of patients having seizure recurrence between 10 minutes and 4 hours after study drug administration was 38.1% for MDZ and 59.7% for placebo ($P = .0043$). The time-to-next seizure occurring more than 10 minutes after receiving study drug was 2.6 hours for MDZ and 0.9 hours for placebo patients (25th percentile results; median time-to-next seizure was not calculable because <50% of MDZ patients had a second seizure within 24 hours). An open-label extension trial of the above study showed that over a median of 16.8 months, these patients tolerated in-MDZ well with no evidence of the development of tolerance.[6]

Other smaller studies have been reported on in-MDZ. The current study's authors published a similar study of 75 adolescents and adults undergoing VEEG between 2008 and 2014 and found similar results.[4] An earlier study compared in-MDZ to diazepam rectal solution for the treatment of seizure exacerbations in a residential epilepsy center[7] and found no differences in efficacy, adverse events or time-to-effect between the 2 ASMs, but the nasal spray was preferred over the rectal formulation by the majority of caregivers and patients.

A commercial form of in-MDZ was approved for use by patients aged ≥12 years by the US Food and Drug Administration in 2019. Additionally, a commercial form of IN diazepam using a new Intravail technology to enhance nasal drug absorption was approved for patients aged ≥6 years in 2020.[8,9] These 2 new products will be valuable options for patients during seizure clusters. The present study[3] is important because the inpatient location not only permitted corroboration of the effectiveness of in-MDZ reported in earlier studies but also provided accurate data both on the duration of effectiveness and on the length of post-dose sedation.

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