



Transnasal Revolution? The Promise of Midazolam Spray to Prevent Seizure Clusters

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In epilepsy patients with repetitive, prolonged seizures or status epilepticus, rapid and effective antiseizure treatment is recommended according to current guidelines (clinical guideline (CG137) for epilepsy). This recommendation is based on evidence that (1) with every epileptic seizure there is an increasing likelihood of recurrent seizures [1]; (2) seizure duration correlates with the risk of seizure transformation into status epilepticus [2]; and (3) status epilepticus is associated with serious cerebral and systemic sequelae [3]. The results from several randomized trials [4–7] emphasize benzodiazepines, such as lorazepam, diazepam, midazolam, and clonazepam as first-line antiseizure drugs. Despite the undeniable need for immediate antiseizure treatment, the rapid administration of benzodiazepines faces many challenges: Intravenous routes can be difficult to establish in the acute setting, subcutaneous intramuscular injections bear the disadvantage of slow drug absorption and pharmacodynamic variability, rectal drug administration is accompanied by social awkwardness and a sense of shame, and the buccal pathway is often hampered by jaw clenching, hypersalivation, or uncontrolled swallowing [8]. These limitations are likely to result in inconsistent use of benzodiazepines, especially in the acute prehospital setting [9, 10], and call for a more secure, reliable, and faster pathway for the administration of emergency first-line antiseizure treatment in the acute setting.

That said, it seems more than plausible that the transnasal application of benzodiazepines offers a new minimally invasive and rapid antiseizure treatment option. Transnasal midazolam may optimize first-line antiseizure treatment by shortening time to drug administration and increase the use of benzodiazepines with the greater ease of use. While pharmacokinetics and pharmacodynamics are well studied [11], data regarding the safety, tolerability, and efficacy of transnasal midazolam in adults are scarce, and are restricted to small [12] and predominantly pediatric cohorts [13, 14].

In this issue of *CNS Drugs*, the German study group of Dr. Strzelczyk present a retrospective two-center study analyzing the efficacy, tolerability, and safety of transnasal midazolam during video electroencephalography (EEG) monitoring with seizures [15]. This study follows their first investigation on the efficacy and tolerability of transnasal midazolam as first-line in-hospital treatment of status epilepticus in adult patients during continuous EEG monitoring, revealing that transnasal midazolam is effective and well-tolerated [16]. In their current study, they carefully performed an intraindividual comparison of seizures with and without the administration of intranasal midazolam in 171 adult patients during continuous EEG monitoring. Seizure recurrence was depicted in survival curves, and Cox proportional hazard models for both the transnasal midazolam and the control groups were performed using a clustering for individual patients. Their analyses revealed that intranasal midazolam significantly reduced the occurrence of repetitive seizures during an observation period of 24 h, and that intranasal midazolam was well-tolerated, without major adverse events. The authors conclude that intranasal midazolam is a safe and efficient treatment option to prevent short-term recurrence of seizures.

There are limitations that need to be mentioned, such as the retrospective study design and the restriction to patients having presurgical evaluations or those suspected of having an epilepsy syndrome. Despite these limitations, these results deserve greater attention as they add credibility to

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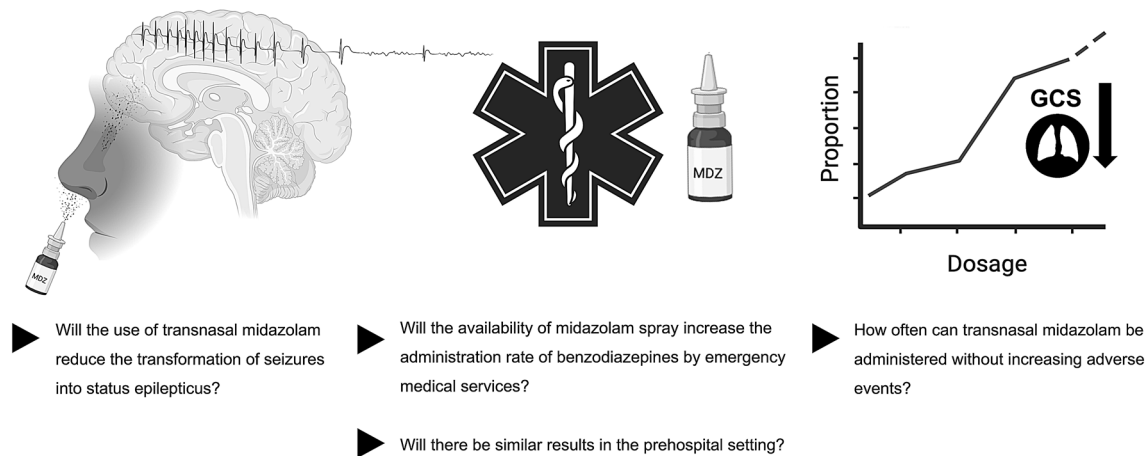


Fig. 1 Outstanding questions regarding the use of transnasal MDZ. *GCS* Glasgow Coma Scale, *MDZ* midazolam

the limited body of evidence that transnasal administration of midazolam offers a safe, well-tolerated, and efficient yet underappreciated emergency treatment option for reducing seizure clusters after the index seizures. There are, however, several questions that need to be answered, to strengthen the evidence for the use of transnasal midazolam as compiled in Fig. 1.

With these questions in mind, researchers, physicians, and emergency medical services are urged to pay close attention to these results with a heightened awareness of potential inappropriate first-line antiseizure treatment. The transnasal route may revolutionize early emergency antiseizure treatment!

Compliance with Ethical Standards

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