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The Winner by a Nose: Intranasal Midazolam

Safety and Efficacy of Midazolam Nasal Spray in the Outpatient Treatment of Patients With Seizure Clusters—A Randomized, Double-Blind, Placebo-Controlled Trial.

Detyniecki K, Van Ess PJ, Sequeira DJ, Wheless JW, Meng TC, Pullmnaan WE. *Epilepsia*. 2019. doi:10.1111/epi.15159. Epub ahead of print.

Objective: To evaluate the safety and efficacy of a novel formulation of midazolam administered as a single-dose nasal spray (MDZ-NS) in the outpatient treatment of patients experiencing seizure clusters (SCs). Methods: This was a phase III, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT01390220) with patients aged $\geq$12 years on a stable regimen of antiepileptic drugs. Following an in-clinic test dose phase (TDP), patients entered an outpatient comparative phase (CP) and were randomized (2:1) to receive double-blind MDZ-NS 5 mg or placebo nasal spray, administered by caregivers when they experienced an SC. The primary efficacy end point was treatment success (seizure termination within 10 minutes and no recurrence 10 minutes to 6 hours after trial drug administration). Secondary efficacy end points were proportion of patients with seizure recurrence 10 minutes to 4 hours and time to next seizure $>$10 minutes after double-blind drug administration. Safety was monitored throughout. Results: Of 292 patients administered a test dose, 262 patients were randomized and 201 received double-blind treatment for an SC (n = 134 MDZ-NS, n = 67 placebo, modified intent-to-treat population). A significantly greater proportion of MDZ-NS than placebo-treated patients achieved treatment success (53.7% vs 34.4%; $P = .0109$). Significantly, fewer MDZ-NS- than placebo-treated patients experienced seizure recurrence (38.1% vs 59.7%; $P = .0043$). Time-to-next seizure analysis showed early separation (within 30 minutes) between MDZ-NS and placebo that was maintained throughout the 24-hour observation period (21% difference at 24 hours; $P = .0124$). Sixteen (5.5%) patients discontinued because of a treatment-emergent adverse event (TEAE) during the TDP and none during the CP. During the CP, 27.6% and 22.4% of patients in the MDZ-NS and placebo groups, respectively, experienced $\geq$1 TEAE. Significance: The MDZ-NS was superior to placebo in providing rapid, sustained seizure control when administered to patients experiencing an SC in the outpatient setting and was associated with a favorable safety profile.

Commentary

This is a report of a large, placebo-controlled, randomized trial of midazolam (MDZ) given intranasally (MDZ-IN) by prefilled atomizer for seizure clusters. Patients 12 years of age and older were given 2 open-label test doses, 5 mg each, 10 minutes apart, in the clinic and then observed for side effects. Sixteen of 292 patients were not randomized because the test dose caused adverse events. Two of these 16 had "events likely indicative of clinically meaningful respiratory depression." One had an intercurrent seizure and the other had preexisting sleep apnea. Other side effects were minor and included nasal discomfort and sedation. Eventually 174 patients were randomized to MDZ-IN and 88 to placebo. One hundred thirty-four patients then received MDZ-IN during the double-blind phase and 67 received placebo spray. A second dose, which always contained 5 mg of the active drug, was allowed if needed.

The primary outcome measure was the combination of seizure termination within 10 minutes of the dose and no recurrent seizures for 6 hours. Of all treated patients, 53.7% of midazolam-treated patients and 34.4% of placebo-treated patients achieved this outcome. Seizures usually stopped within 10 minutes in both groups (80.6% for MDZ-IN and 70.1% for placebo). At least one more seizure recurred within 6 hours in 41.8% of the MDZ-IN group and 62.7% of the placebo group.

What are seizure clusters (also known as "acute repetitive seizures") and why is it important to treat them? This term defies easy definition,[1] but if patients or families recognize a phenomenon as a cluster, then operationally it is a cluster.

You know it when you see it. An underrecognized difficulty with the definition is that many seizures, in a statistical sense, are part of a cluster. Seizures do not occur randomly in a Poisson distribution. Seizure diary data indicate that occurrence of a seizure makes a seizure on the next day more, not less, likely.[2] This rule probably holds over other time domains. That is, seizures beget seizures, not just over periods of days and years but also over periods of hours. Seizure clusters are also common: In one study, 43% of patients were judged to have cluster by clinical or diary data and 22% by a stricter statistical definition.[3]

This leads to a second conclusion: It is important to stop seizure clusters, not only because of the impairment of function but also to prevent progression to status epilepticus. Patients reporting seizure clusters are 3.7 times more likely to have experienced status epilepticus than those whose seizures are more isolated in time.[4] Patients rightly fear that one seizure may lead shortly to another, then another.

The need for "rescue" medications for seizure clusters is clear. Should MDZ be the rescue medication of choice, and should the nasal route be preferred? Because of differing definitions, doses, and outcome measures, it is difficult to compare the results between different benzodiazepines (BDZs) and delivery methods. The previous Food and Drug Administration (FDA)-approved drug for clusters is rectal diazepam (DZP), In Europe, buccal MDZ is also approved. There have been several comparative trials between 2 BDZs, but most have been open label. A useful review of these trials and of relevant BDZ pharmacokinetics is available.[5] In direct comparisons of intranasal MDZ with rectal DZP, outcomes were similar.[3,6] My interpretation of the results of these trials is that, if an adequate dose of drug reaches the brain with equal quickness, all BDZs are equivalent in their ability to stop a seizure cluster. The choice depends more upon ease of use and duration of action.

MDZ-IN has advantages. The time to peak level is less than 10 minutes. The downside is that it has a short elimination half-life of 1.5 to 6 hours. But this may not be the most important factor if the goal is to break up the progression to accelerating seizures or to status epilepticus.

This study provides class I evidence that MDZ-IN is superior to placebo for the treatment of seizure clusters. The numerical difference from placebo is a little disappointing: 2 in 5 MDZ-treated patients had a recurrent seizure within 6 hours compared to 3 in 5 for placebo. However, for this one person in 5, the effect may be critical, even more so when we consider that clusters commonly recur in some patients. Each cluster presents a small but definite risk of progressing to status epilepticus.

Why has it taken so long for regulatory approval of rescue BDZs?

Midazolam was formulated at about the time the first man stepped on the moon. Reports of intranasal MDZ for sedation for minor surgical procedures in children were numerous by the late 1970s. A possible use for epilepsy was suggested by observation of electroencephalography spike suppression in 6 patients in 1986,[7] but it took many more years for this use to attract attention.[8] Since then there have been at least 10 clinical trials, though many were nonrandomized or nonblinded.[5] There are reasons for this delay other than a lack of serendipity. The vicissitudes of mounting a clinical trial for seizure clusters are daunting. Benzodiazepines are generic, so a formulation of some added value was necessary to spur commercial development.

In the interim, other routes and drugs have been tried. The US Army deployed intramuscular DZP syringes, 10 mg each, for cholinergic-induced seizures in the mid-1990s, though fortunately their efficacy was never put to the test. There were also clinical trials for civilian use.[9] Buccal midazolam has grown in popularity. The buccal route works well, but if swallowed, MDZ is largely inactivated by first-pass metabolism. Lorazepam can be given buccally, but should be refrigerated, while MDZ is stable in aqueous solutions.

With clinical experience, we may be able to do better. The dose used in the double-blind portion of this MDZ-IN trial was 5 mg, but 10 mg within 10 minutes was tolerated by most of the patients in the open-label portion. There is still a place for other drugs and other methods. A trial is currently underway for inhaled alprazolam.[10] Intramuscular injections are usable by medical personnel and by some families. If there is preexisting intravenous access, that may remain the gold standard. In any case, there are now compelling alternatives to oral lorazepam, which is cheap and simple, but far too slow for many seizure clusters.

Midazolam given intranasally is not a magic bullet for acute seizures, but we should be grateful that the results of this difficult trial were positive. A commercial version of MDZ-IN was approved by the FDA in May 2019, thus winning the race for a more practical acute BDZ preparation by a nose.

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