

## Intranasal Administration of Benzodiazepines for the Treatment of Acute Repetitive Seizures in Children

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Administration of antiepileptics in children with acute repetitive seizures outside of the hospital setting is often difficult. At the present, only rectal diazepam has been approved by the Food and Drug Administration (FDA) for use in these situations. This formulation, however, is expensive and difficult for many parents to administer, especially during seizures occurring outside the home. Many older children and adolescents object to this route as being intrusive and socially unacceptable. A growing number of studies have documented the safety and efficacy of alternative routes for giving antiepileptics, such as intranasal, intramuscular, or buccal administration.<sup>1-3</sup> This issue of the newsletter will focus on recent studies evaluating intranasal administration of benzodiazepines in children in the home, prehospital, and hospital settings.

### Intranasal Administration

The availability of inexpensive disposable nasal atomizers has made the use of this route more feasible. Mucosal atomization devices (MADs), such as the LMA MAD Nasal™, use a small cone-shaped flexible atomizer attached to a standard disposable luer lock or slip tip syringe to allow for accurate dose measurement and delivery. The size of the particles generated varies based on the speed and force of compression of the syringe plunger. Mean particle size is approximately 60 microns, which promotes deposition over a broad area of the nasal mucosa. The device has a dead space of approximately 0.1 mL, which must be taken into account for small doses.<sup>2,4,5</sup>

The rapid delivery of drug to central nervous system achieved after intranasal administration, as well as the ability to bypass gastric and hepatic first-pass metabolism, make this route an effective alternative to IV, IM, buccal, or rectal benzodiazepine administration. The use of concentrated injectable solutions, such as the 5 mg/mL concentration of midazolam, is preferable for minimizing the volume administered and avoiding nasal run-off. The

major disadvantage of intranasal administration is the susceptibility to physiologic changes in the mucosa, due to allergic rhinitis or respiratory infections, which can reduce drug absorption.<sup>2,5,6</sup>

### Midazolam

The physical and pharmacokinetic properties of midazolam make it well suited for intranasal administration. It is soluble in water at an acidic pH, but becomes more lipophilic as pH rises which allows for the rapidity at which it crosses the blood-brain barrier.<sup>1,2</sup> In 1991, Rey and colleagues compared the pharmacokinetic profile of intranasal and IV midazolam in 12 children between 1 and 5 years of age.<sup>7</sup> The children were randomized to receive a single 0.2 mg/kg dose by one of the two routes. Estimated bioavailability of the intranasal route was 55%, with a mean time to maximum plasma concentration of  $12 \pm 4$  min. Mean maximum concentration in the intranasal midazolam group was  $104 \pm 32$  mcg/L, lower than that achieved with IV use ( $382 \pm 59$  mcg/L). Mean elimination half-life was similar in the two groups:  $2.22 \pm 1.19$  hrs in the intranasal group and  $2.37 \pm 1.55$  hrs with IV administration. Apparent volume of distribution ( $4.12 \pm 2.16$  L/kg) and clearance ( $1.44 \pm 0.52$  L•hr<sup>-1</sup>•kg<sup>-1</sup>) following intranasal administration were approximately twice the values obtained after IV administration.

Beginning with the first publications in the mid-1990s, the utility of intranasal midazolam has been evaluated in more than four dozen papers, including open-label, placebo-controlled, and comparison studies. In a recent review in *The Journal of Pediatric Pharmacology and Therapeutics*, Humphries and Eiland described three open-label intranasal midazolam studies in children and four studies comparing it to rectal diazepam.<sup>6</sup> The rate of successful termination of seizures in open-label studies with intranasal midazolam has ranged from 80 to 100%.<sup>4,6,8</sup> The comparison studies published to date have consistently demonstrated time to seizure cessation with intranasal midazolam equivalent to or better than that of standard therapies.<sup>6,9-14</sup>

Fisgin and colleagues published one of the earliest comparison studies with intranasal midazolam in pediatric patients.<sup>9</sup> In 2002, the authors conducted a randomized study of rectal diazepam (0.3 mg/kg) and intranasal midazolam (0.2 mg/kg) given by a dropper in 45 infants and children ranging in age from 1 month to 13 years. If seizures continued after 10 minutes, the alternative drug could be administered. The children were observed for 1 hour. If seizures persisted or recurred, IV midazolam was given. Eighty-seven percent of the children receiving intranasal midazolam had resolution of their seizures within 10 minutes, compared to only 60% of those given rectal diazepam ( $p < 0.05$ ). Forty-one percent of the patients initially treated with diazepam needed additional antiepileptics, compared to only 12% of those given midazolam as their first agent ( $p < 0.05$ ).

A similar study was published in 2006 by Bhattacharyya, Kalra, and Gulati in *Pediatric Neurology*.<sup>10</sup> Forty-six children (3 months-12 years of age) were treated for a total of 188 seizure episodes in this randomized, single-blind study. As in the previous study, patients received either rectal diazepam (0.3 mg/kg) or intranasal midazolam (0.2 mg/kg) by dropper for acute seizures in the clinic or emergency department. The time required for drug administration was significantly shorter with intranasal midazolam (50.6 sec versus 1.14 min,  $p = 0.002$ ). Mean time from drug administration to cessation of seizures was also shorter in the midazolam group ( $1.95 \pm 2.12$  min) than in the diazepam group ( $2.98 \pm 2.99$  min,  $p = 0.005$ ). Mean heart rate and blood pressure did not differ between the groups. Respiratory rate, however, decreased to a greater degree in the rectal diazepam group at both 10 and 30 minutes ( $p = 0.027$  and  $p = 0.039$ ).

Two additional studies from Holsti and colleagues at the University of Utah evaluated the efficacy and safety of intranasal midazolam administered by emergency medicine services (EMS) personnel in the prehospital setting or by family members in the home. In 2007, the authors compared the results from a new EMS protocol using intranasal midazolam (0.2 mg/kg) delivered with a MAD to data obtained prior to the new protocol when rectal diazepam (0.3-0.5 mg/kg) was used as first-line therapy for seizures lasting longer than 5 minutes.<sup>11</sup> A total of 124 children up to 18 years of age were treated. The median duration of seizures was significantly longer in the rectal diazepam group than in the midazolam group (30 min versus 11 min,  $p = 0.003$ ). The need for additional antiepileptics, as well as frequency of intubation, the number of patents requiring hospital and intensive care unit admission, were significantly greater in the rectal diazepam group. These factors led to a higher mean total hospital charge with rectal diazepam (\$6,980 versus \$1,459 in the midazolam patients,  $p < 0.0001$ ).

The authors found similar advantages with intranasal midazolam compared to rectal diazepam for breakthrough seizures in the home.<sup>12</sup> They randomized families of 358 pediatric seizure patients treated in their clinic to receive either intranasal midazolam 0.2 mg/kg given via a MAD (maximum dose 10 mg) or rectal diazepam 0.3-0.5 mg/kg (maximum dose 20 mg) for any seizure lasting more than 5 minutes. Ninety-two caregivers gave a dose of the study medication. The median time from administration to cessation of seizures was 3 min for intranasal midazolam compared to 4.3 min with rectal diazepam ( $p = 0.09$ ). There were no differences in adverse effects, the need for hospitalization, or the need for intubation and mechanical ventilation, although the number of patients requiring emergency services was slightly higher in the midazolam group. Caregivers for the children given midazolam rated ease of dose administration and their overall satisfaction higher than those in the diazepam group.

Similar results were seen in a comparative study of intranasal midazolam and IV diazepam conducted by Javadzadeh and colleagues in 60 children (2 months to 15 years of age) seen in an emergency department in Tehran.<sup>13</sup> The children were randomized to receive either 0.2 mg/kg midazolam dripped into the nares or 0.3 mg/kg IV diazepam. As in the previous studies, time from drug selection to seizure cessation was significantly shorter with intranasal midazolam than with IV diazepam (mean  $3.16 \pm 1.24$  min versus  $6.42 \pm 2.59$  min,  $p < 0.001$ ). There were no differences in oxygen saturation or heart rate, and no cases requiring intubation.

Earlier this year, Thakker and Shanbag conducted an additional study comparing intranasal midazolam to IV diazepam for acute seizures in children seen in a pediatric emergency department in Mumbai.<sup>14</sup> Fifty children (1 month to 12 years of age) were randomized to receive either 0.2 mg/kg midazolam dripped into the nares or 0.3 mg/kg IV diazepam for a seizures lasting more than 10 minutes. The primary outcome measures were time from arrival to initiation of treatment and time from arrival to seizure cessation. As noted in earlier studies, time to treatment was significantly shorter in the midazolam group (mean  $3.37 \pm 2.46$  min versus  $14.13 \pm 3.39$  min in the diazepam group). Time from arrival to cessation of seizures was also significantly shorter with midazolam than with diazepam ( $6.67 \pm 3.12$  versus  $17.18 \pm 5.09$  min). However, the time for drug response (the interval between drug administration and cessation of seizures) was shorter in the diazepam group ( $2.67 \pm 2.31$  min) compared to the midazolam group ( $3.01 \pm 2.79$  min, all comparisons  $p < 0.05$ ). Three patients in each group had recurrence of their seizures requiring additional treatment. There

were no significant adverse effects in either group, but one child given diazepam had evidence of respiratory depression.

While these studies provide convincing evidence of the benefits of intranasal midazolam, the steps involved in preparing the dose and the difficulty in obtaining injectable products at some retail pharmacies limit its utility outside of the hospital. A new intranasal midazolam product being developed by Upsher-Smith Laboratories may reduce this burden for families. Preliminary results from a phase 1 pharmacokinetic, pharmacodynamics study in healthy volunteers, presented at the 2013 annual meeting of the American Academy of Neurology, demonstrated a time to maximum plasma concentration of 10-15 minutes. A global phase 3 randomized, double-blind, placebo-controlled safety and efficacy trial of their product is currently underway.<sup>15</sup> A total of 155 patients from 14 to 65 years of age are expected to be enrolled at 73 study sites. Primary outcome measures are the percentage of patients who achieve termination of seizures within 10 minutes of drug administration and the percentage of patients who remain seizure-free for 4 hours. The estimated time for completion of the study is December 2013. A phase 2a open-label extension study is also underway to evaluate long-term effects after multiple uses.<sup>16</sup> The anticipated completion date for this study is September 2014.

#### Lorazepam

Although not as widely studied as midazolam, intranasal lorazepam may be another useful option for the treatment of acute seizures. Pharmacokinetic studies of this route have not yet been conducted in children, but studies in adults have documented a bioavailability of approximately 77% and a mean time to maximum serum concentration of  $105 \pm 75$  min after a 2 mg intranasal lorazepam dose.<sup>17,18</sup> In addition to a longer time to peak concentration, lorazepam injection also requires refrigeration, making it less suitable for EMS transport or for families when traveling.

In a 2011 randomized open-label study of 141 children, Arya and colleagues found a similar response between intranasal and IV lorazepam.<sup>19</sup> The children (6-14 years of age) were randomized to either a 0.1 mg/kg (maximum 5 mg) dose of either IV or intranasal lorazepam following initial stabilization in a New Delhi emergency department. The two routes produced very similar results. Remission of clinical seizures occurred within 10 minutes in 80% of the IV group and 83.1% of the intranasal group. Fifty-eight percent of children in the IV group and 62% in the intranasal group remained seizure-free for the full 1 hour evaluation period ( $p = 0.68$ ).

Ahmad and colleagues compared intranasal lorazepam to IM paraldehyde in children over 2 months of age seen in a pediatric emergency department in Malawi for prolonged seizures.<sup>20</sup> A total of 160 children were randomized to receive either intranasal lorazepam 0.1 mg/kg or IM paraldehyde 0.2 mL/kg. Seventy-five percent of the children treated with intranasal lorazepam had cessation of their seizures within 10 minutes, compared to 81% of those given paraldehyde. Neither group experienced serious adverse effects. The authors considered the two groups equally effective, but highlighted the ease of use with the intranasal route.

#### Diazepam

Diazepam has also been considered for intranasal use, but its physical properties may limit its utility. The IV formulation has a relatively low bioavailability when given intranasally. Early studies also found it was not well tolerated when given intranasally.<sup>1</sup> Alteration of the drug vehicle may improve these issues. Two studies published earlier this year from the Center for Orphan Drug Research at the University of Minnesota describe the efficacy and tolerability of several investigational intranasal diazepam products.<sup>21,22</sup>

Ivaturi and colleagues enrolled 12 healthy adult volunteers into a double-blind, crossover pharmacokinetic study of intranasal and rectal diazepam.<sup>21</sup> All subjects received the three intranasal products evaluated (two providing a 10 mg dose and one providing a 13.4 mg dose) as well as a 10 mg rectal dose, with each dose separated by a 14-day washout period. The bioavailability of the intranasal products ranged from 70% to 89%. Mean maximum plasma concentrations were  $151.3 \pm 108.1$  and  $181.8 \pm 84.16$  ng/mL for the two 10 mg intranasal doses, and  $180.7 \pm 82.1$  ng/mL for the 13.4 mg/mL dose, similar to the level produced by the standard 10 mg rectal dose,  $160.9 \pm 109.4$  ng/mL. Mean time to maximum concentration was 0.75 hrs in all groups. Tolerability was assessed with pain, sedation, and nasal irritation scores. Mean pain scores for all intranasal doses were higher than with the rectal dose (2.6, 1.6, and 1.4 versus 0.3). Sedation scores were similar among the groups, and none of the nasal irritation scores differed from baseline.

Agarwal and colleagues published the results of a pilot study comparing the two new intranasal diazepam formulations (a solution and a suspension) to IV diazepam in healthy adult volunteers.<sup>22</sup> Twenty-four subjects were randomized in this open-label, crossover study comparing the new products to a standard IV dose. Each patient received a 10 mg dose of both of the intranasal preparations and a 5 mg IV dose. Bioavailability was greater with the intranasal solution (97% versus 67% for the suspension). Mean maximum concentrations were similar;  $272 \pm 100$  ng/mL for the

suspension and  $221 \pm 78.6$  ng/mL for the solution. Fifteen of the 24 patients had diazepam concentrations above the 200 ng/mL threshold necessary for seizure control. Mean time to achieve the maximum concentration was 1.5 hr and 1 hr for the suspension and solution. Mean area under the concentration-time curve (AUC) was  $7,340 \pm 1,882$  ng•hr/mL for the intranasal solution, significantly greater than that of the suspension or IV dose ( $5,229 \pm 1,463$  ng•hr/mL and  $3,832 \pm 1,150$  for ng•hr/mL, respectively,  $p < 0.05$ ). Adverse effects were reported in 71% of patients, primarily somnolence and mild transient epistaxis. The authors concluded that these new formulations provide results similar to IV diazepam.

### Summary

Intranasal administration of benzodiazepines has been shown to be a safe and effective means of managing acute repetitive seizures in children and adolescents. New intranasal delivery devices, as well as the development of new intranasal midazolam and diazepam products, suggest growing interest in alternatives to traditional rectal diazepam and the potential for a wider range of options in the future.

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### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their September meeting:

1. Everolimus (Zortress®) was added to the Formulary for the prevention of rejection in kidney and liver transplant patients.
2. Radium Ra 223 dichloride (Xofigo®) was added for the treatment of patients with refractory prostate cancer and symptomatic bone metastases with no metastatic disease.
3. Doxepin oral solution was added for treatment of oral mucositis pain, with restriction to use by Palliative Care, Radiation Oncology, and Hematology/Oncology.
4. Sodium phosphate enema (Fleet's enema) was removed from the Formulary.

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