Hyponatremic Seizure in a Child Using Desmopressin for Nocturnal Enuresis

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**Background:** Intranasal desmopressin has been used extensively to treat primary nocturnal enuresis. While it has proven to be a safe, effective agent for many who are affected by this condition, the potential for complications exists.

**Objectives:** To report a case of severe hyponatremia associated with a generalized tonic-clonic seizure in a 10-year-old boy who had been receiving intranasal desmopressin nightly for nocturnal enuresis and to briefly review therapeutic options for nocturnal enuresis; and to present the role of desmopressin.

**Setting:** Georgetown University Medical Center, Washington, DC.

**Intervention:** Fluid restriction and intravenous isotonic saline solution with 5% dextrose was administered to raise the serum sodium level.

**Outcome:** Prevention of further seizures with normalization of serum sodium levels without any obvious neurological sequelae.

**Conclusions:** This case illustrates the importance of weighing the benefits and risks of intranasal desmopressin therapy.

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Intranasal desmopressin acetate is a common therapy for primary nocturnal enuresis. While intranasal desmopressin has proven to be a safe and effective agent for many who suffer from this condition, the potential for serious complications exists. We report a case of severe hyponatremia associated with a generalized tonic-clonic seizure in a 10-year-old boy receiving intranasal desmopressin nightly for 3 weeks for nocturnal enuresis.

**Outcome**

The boy was admitted to the pediatric intensive care unit and fluid intake was restricted. Subsequent fluid balance and laboratory studies are presented in the table.

Despite fluid restriction, the serum sodium level decreased to 117 mmol/L 3 hours after his initial presentation. Intravenous isotonic saline solution with 5% dextrose was administered to slowly raise the serum sodium level. With this intervention, the serum sodium level increased to 120 mmol/L during the next 11 hours. Four hours later, the boy’s urine output increased, and the serum sodium level increased to 131 mmol/L. Treatment with intravenous fluids was discontinued and the boy was allowed to eat. By the time of discharge from the hospital, urine osmolality had decreased to 263 mmol/kg H₂O, serum osmolality had increased to 277 mmol/kg H₂O, and serum sodium levels had risen to 134 mmol/L. No further seizure activity was observed, and the dysarthria and myoclonic jerks that were initially noted gradually resolved over the course of the boy’s brief hospitalization.

Two sets of serum electrolyte levels, drawn 5 days and again 2 weeks after his discharge from the hospital, were within reference ranges. Months after his seizure, his pediatrician reports that the patient is doing well, without any obvious neurological sequelae. He has not resumed intranasal desmopressin therapy for his nocturnal enuresis.

**Comment**

Primary nocturnal enuresis may be defined as urinary incontinence during sleep in a patient who has never been consistently continent and who has reached an age when the majority of children have achieved bladder control.† Five to 7 million children in the United States are diagnosed with primary nocturnal enuresis. The child with primary nocturnal enuresis typically has normal daytime voiding patterns and does not have an underlying psychiatric or organic illness. Enuresis usually resolves spontaneously and has no long-term physical side effects. However, children affected by enuresis are often distressed by their problem. Their families experience a considerable amount of stress.\(^ {2,3} \)
An enuretic 10-year-old boy presented to the emergency department after experiencing a brief generalized tonic-clonic seizure. He had been well until 24-hours prior to his admission to the hospital, when he became nauseated and experienced 2 hours of emesis. He was evaluated by his pediatrician, who prescribed cefadroxil, 500 mg/d, after a rapid antigen test confirmed the diagnosis of streptococcal pharyngitis. After taking 1 dose of cefadroxil, his symptoms improved. He rested comfortably until the following morning, when he vomited once again, and then had a seizure.

The boy's mother reported that he had been receiving 40 µg of intranasal desmopressin nightly for 3 weeks for primary nocturnal enuresis. She confirmed that the intranasal desmopressin had been administered as prescribed. Cefadroxil was the only other medication being used. The boy and his mother were pleased with the results achieved with intranasal desmopressin. He had not experienced enuresis or suffered any adverse side effects while taking the medication. There was no history of excessive fluid intake, diarrhea, or fever prior to experiencing the seizure. Electrolyte levels, drawn prior to the initiation of intranasal desmopressin therapy, were within reference ranges. Aside from the boy's history of nocturnal enuresis, his medical history was unremarkable; he did not have a history of head trauma, birth trauma, meningitis, or seizures. There was no family history of a seizure disorder.

Initial vital signs revealed a temperature of 36°C; heart rate of 83 beats/min; respiratory rate of 16/min; and blood pressure of 140/78 mm Hg. There was no evidence of trauma or of respiratory or cardiovascular compromise. Mucous membranes were moist, good skin turgor was noted, and there was no peripheral edema. The boy was noted to be drowsy with mild dysarthria and intermittent myoclonic jerking of his hands. Findings from the remainder of his neurologic examination were nonfocal. A computed tomographic scan of the head showed no abnormalities. Values for serum glucose, calcium, magnesium, and uric acid were normal. A complete blood cell count was normal. However, a serum sodium level of 121 mmol/L and urine specific gravity of 1.029 were measured.

There are many approaches to therapy for primary nocturnal enuresis. Many advocate simply waiting for spontaneous resolution of symptoms. Psychological counseling and hypnosis have been beneficial treatments for the minority of patients who have underlying behavioral problems or mental illness. Motivational therapy, which involves providing positive reinforcement for dry nights, is relatively ineffective when used alone, but it can be helpful when combined with other treatment modalities. Enuresis alarms condition patients to recognize bladder fullness while asleep and have been credited with a long-term cure rate, as high as 70% when used consistently for 3 to 4 months. Disadvantages of this method include a low compliance rate and the length of time that it takes to be effective.

Pharmacologic therapy is preferred by many physicians and families due to its relative ease of use and quick onset of action. Tricyclic antidepressants, such as imipramine, have been used extensively since the 1960s. While imipramine hydrochloride has been proven to be effective in a large percentage of patients, there are frequent relapses when patients cease taking the medication. In addition, the potential for serious side effects, such as arrhythmias, convulsions, and coma have limited its use for the treatment of enuresis.

Intranasal desmopressin is a vasopressin analog that has been used for decades to treat diabetes insipidus, von Willebrand disease, and hemophilia A. Since its approval in the 1980s as a treatment for primary nocturnal enuresis, intranasal desmopressin has proven to be effective for many patients. Researchers have shown that a large proportion of patients with enuresis secrete inadequate amounts of antidiuretic hormone during the night, resulting in higher urine production, decreased urine osmolality, and reduction in functional bladder capacity. Intranasal desmopressin counteracts this by increasing free water absorption at the nephron, thus decreasing urine volume. Effects begin within 1 to 2 hours after administration, and its duration of action ranges from 6 to 24 hours.

Numerous studies have been conducted to evaluate the effectiveness of intranasal desmopressin, and most have demonstrated a statistically significant improvement in patients' symptoms. Relapse rates, however, are high after treatment with the medication has been discontinued. Intranasal desmopressin is generally well tolerated. Nasal irritation, headache, nausea, mild abdominal cramps, and dizziness are known side effects. There does not appear to be depression of endogenous antidiuretic hormone secretion with the use of intranasal desmopressin.

Reports of electrolyte imbalances resulting from the use of intranasal desmopressin are uncommon. Williford et al described reports of 10 children and 2 adults who experienced hyponatremia and seizures while using intranasal desmopressin. Seven of these patients (6 of whom were children) were prescribed intranasal desmopressin for primary nocturnal enuresis. In each case, there were complicating factors that helped to explain why each patient developed hyponatremia. For example, a 10-year-old boy who had been using intranasal desmopressin for 3 days experienced a seizure after drinking excessive amounts of water for 1 day to treat hiccups. A 28-month-old boy receiving intranasal desmopressin had a seizure after being given extra liquids by his parents to calm him. Another child who had a 2-year history of intranasal desmopressin use experienced a seizure 2 days after restarting treatment with intranasal desmopressin after a 2-month hiatus from the medication. It was thought that he demonstrated an exaggerated response to the medication due to up-regulation of receptors. One child had cystic fibrosis and nasal polyps; it was thought that variable absorption of intranasal desmopressin from her condition may have contributed to her hyponatremia. Two children received doses in excess of the prescribed amount prior to having seizures. Finally, a 10-year-old boy who had been using intranasal desmopressin for 7 months experienced a seizure after imipramine was added to improve his nocturnal enuresis.

In contrast to previously reported cases of hyponatremic seizures associated with the use of intranasal desmopressin in nocturnal enuresis, we believe this case is unique in several respects. (1) This patient did not have

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Fluid Balances and Laboratory Studies

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<th>Time Elapsed Since Intranasal Desmopressin Dose, h:min</th>
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<th>Cumulative Urine Output, mL</th>
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* Emergency department admission.
† ND indicates not done.
‡ Treatment with intravenous fluids started.
§ Treatment with intravenous fluids stopped; patient allowed to eat and drink normally.

a history of excessive fluid intake. (2) He was examined by his pediatrician less than 24 hours prior to experiencing his seizure and was not found to have physical signs of hypervolemia. (3) He and his mother were adamant that the medicine had been given correctly. Multiple health care workers, including the patient’s primary pediatrician, interviewed the family to verify this crucial part of the history. Unlike the child with cystic fibrosis who experienced a seizure while receiving intranasal desmopressin therapy, our patient was essentially a well child, with the exception of a mild, self-limiting illness due to group A streptococcal infection. He did have 2 bouts of emesis prior to experiencing the seizure; however, if these episodes altered his fluid balance, the effect would have made him mildly hypovolemic, causing hypernatremia rather than dilutional hyponatremia. Finally, he was not taking any medications that are known to enhance or prolong the effect of intranasal desmopressin.

This case illustrates the importance of weighing the benefits and risks of intranasal desmopressin therapy, as well as ways that physicians can help minimize these risks for their patients. The recommended dose of intranasal desmopressin for the treatment of nocturnal enuresis ranges from 20 to 40 µg nightly. The initial regimen for the patient described in this report was 40 µg per night. A more conservative approach that might minimize possible side effects would be to initiate therapy with a dose of 20 µg nightly. This dose may be increased by 10-µg increments up to a maximum of 40 µg if the initial regimen proves ineffective. Conversely, a patient who responds well to the 20-µg regimen may derive equal benefit from 10 µg nightly; therefore, a trial of half the initial dose would be worthwhile. Measurement of serum electrolytes in patients with enuresis who are otherwise healthy prior to the initiation of intranasal desmopressin is of negligible benefit in the identification of those who are at risk of electrolyte imbalance from intranasal desmopressin therapy. The manufacturer recommends monitoring electrolyte levels at least once during intranasal desmopressin therapy if its use extends beyond 1 week. In addition, it is prudent to monitor electrolyte levels in patients with intercurrent illnesses that might affect hydration status or alter drug absorption. Water intoxication may cause a variety of nonspecific symptoms. Some patients may complain of apathy, nausea, vomiting, decreased appetite, muscle cramps, and weakness; others may present with delirium, coma, or seizures.10,13 Clinicians should have a low threshold for screening patients for intranasal desmopressin toxicity when they present with any of these symptoms. It is possible that our patient’s episodes of vomiting were symptoms of altered fluid balance rather than a sequela of his streptococcal infection. Finally, given the potential risks of therapy and limited long-term benefit of pharmacologic intervention, nonpharmacologic treatment options should be given careful consideration prior to the institution of pharmacologic therapy.

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REFERENCES