Intranasal Desmopressin-Associated Hyponatremia: A Case Report and Literature Review

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We present a case of a 29-year-old woman with a long history of nocturnal enuresis who developed symptomatic hyponatremia from water intoxication shortly after beginning desmopressin. A MEDLINE search in the English language revealed 13 prior case reports. All patients presented with seizure, mental status changes, or both. Two distinct presentations occurred: one group of patients maintained a stable course with desmopressin and developed symptoms related to an outside factor. The other group of patients were new to desmopressin and had a profound water intoxication response from its use. While the underlying cause was from simple overhydration, the quickness of this unanticipated adverse effect is noteworthy. The importance of counseling to ensure a family's and a patient's understanding of the effects of desmopressin as well as monitoring electrolytes periodically may help identify and prevent this serious iatrogenic complication.

KEY WORDS. Desmopressin; water intoxication; hyponatremia; enuresis. (*J Fam Pract 1997; 44:203-208)*

Desmopressin acetate (DDAVP) is an increasingly used, well-tolerated medicine for the treatment of primary nocturnal enuresis and central diabetes insipidus. Clinical trials have shown that intranasal desmopressin generally provides symptomatic relief with minimal serious complications. While side effects and complications have been generally minimal, they do exist and can be quite severe. Mild and serious complications, including severe hyponatremia, have already been extensively reviewed with intravenous use,[1,2] but few cases have been noted with intranasal use.

The purpose of this article is to present, review, and discuss the complication of profound hyponatremia associated with intranasal desmopressin use.

Case Report

A 29-year-old white woman with a history of nocturnal enuresis was brought to the emergency department by her husband because of a number of symptoms. These included a pressure-like frontal headache, blurring vision, increasing lethargy, confusion, disorientation, nausea and vomiting, periodic waning levels of consciousness, malaise, chills, and diaphoresis. The spouse related that his wife's symptoms, which included a generalized headache, nausea, weakness, and lethargy, began 1 week before presentation. He also related that she was seen in the emergency department 4 days earlier for similar symptoms.

Records from that prior visit revealed no medication use except oxybutynin, no trauma or insect bites, and no other medical problems. Her examination was essentially unremarkable. Her only significant abnormal laboratory study was a sodium level of 127 mmol/L. She was treated with intravenous fluids, felt better, and was discharged to home. When the symptoms worsened 3 days later, her husband brought her back to the emergency department. Her outpatient records revealed a note from the urology service made 11 days earlier, which had reviewed her negative workup for other causes of enuresis and considered beginning treatment with desmopressin. Her husband, however, was not aware of her receiving this medication.

On the night of admission, the patient was stuporous and uncooperative; her speech ranged from slurred to unintelligible. Her vital signs showed mild orthostatic changes, but her examination was otherwise unremarkable. Her laboratory studies were remarkable for depressed serum electrolytes, includ-

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ing a sodium level of 124 mmol/L. A chest radiograph and electrocardiogram were normal. A noncontrast computed tomography scan of the head and cerebrospinal fluid studies were normal. A serum cortisol was normal. Her urine and serum drug screening tests were negative, and her initial urinalysis was normal with a specific gravity of 1.010. A spot urinary sodium was 23 mmol/L, which was mildly elevated.

She was admitted to the intensive care unit for further evaluation, observation, and treatment. She had received 4 L of normal saline while in the emergency department, and her subsequent urinalysis had a specific gravity of 1.001. Her serum electrolytes rose, with a sodium of 137 mmol/L later that night, and 141 mmol/L by morning. A subsequent urinalysis 4 hours after admission had a specific gravity of 1.010 with a urine sodium of 152 mmol/L. Over the night, she was noted to have an excess urine output of approximately 1500 mL compared with her intake. When the patient awoke in the morning, she was quite calm and behaved appropriately. She was able to provide a full history that included starting desmopressin 11 days before admission. She had forgotten to mention that she was taking desmopressin when she came to the emergency department. She never associated it with her symptoms and continued using it every night.

With this additional history, the patient was presumed to have had water intoxication and secondary hyponatremia, most likely due to the desmopressin. She was further evaluated with a 24-hour fluid restriction. Her urine specific gravity rose to 1.025, and her urine sodium level rose to 214 mmol/L. Her serum sodium remained normal. She felt fine, her examination status remained unchanged, and the rest of her studies were within normal limits. Therefore, she was discharged with a diagnosis of drug-induced hyponatremia. She was instructed not to take any more oxybutynin or desmopressin.

Discussion

Nocturnal enuresis is a common childhood illness. Since up to 30% of children may have at least one episode of bed wetting monthly, the diagnosis of nocturnal enuresis and its treatment are not appropriate before the age of 6. The spontaneous cure rate alone averages about 15% per year. Treatment regimens, such as bed wetting alarms, supportive counseling, preplanned times to awaken, and medications, are meant to help improve cure rates. By 12 years of age, approximately 4% of children continue to have enuresis. By age 18, less than 1% continue to be affected, but in these cases enuresis often continues into adulthood.[3,4] The inability of nighttime urinary control as an adolescent or adult can result in a host of psychological problems including low self-esteem, despair, shame, alcoholism, and drug dependency.[5] The use of intranasal desmopressin as therapy for nocturnal enuresis began in the 1980s, and many of these refractory patients achieved success with using desmopressin where all prior modalities had failed.[6,7]

Desmopressin is a synthetic analogue of the human antidiuretic hormone arginine vasopressin. It has been used intravenously in the treatment of central diabetes insipidus, hemophilia A, and von Willebrand's disease. Intranasal desmopressin has been used to treat central diabetes insipidus, to test renal concentrating capacity, and to treat primary nocturnal enuresis[8]. It increases water reabsorption by means of V_2 receptors in the kidney tubule, thereby increasing urine osmolality and decreasing urine volume. This results in an increase in intravascular and tissue volume and a decrease in plasma osmolality. With a mean half-life of approximately 90 minutes, desmopressin acts quickly to decrease the production of urine after the first or second hour. The effect usually lasts 6 to 12 hours, but it may continue up to 24 hours, especially in young children, infants, and geriatric patients.[7,9] Because of its pharmacokinetics, intranasal desmopressin is suited for use at bedtime, when increased water reabsorption results in a smaller overnight volume of urine production. This creates less stretch of the bladder wall during sleep and a decreased risk of spontaneous, spastic release. As the effect of desmopressin wanes, water excretion resumes with a compensatory diuresis, usually during daytime hours when bladder control is stronger and under conscious control.[7,8]

Drug Regimen and Side Effects

The standard starting dose for patients older than 6 years of age is 20 µg, or two 10-µg sprays. If used in children younger than age 6, a single 10-µg spray is recommended. Indications that it is well tolerated by most patients can be found in the literature. If success is obtained in controlling the enuresis at the initial 20-µg dose, a trial of 10 µg at bedtime is recom-

mended. If success is not obtained after 3 days, a trial at 40 µg at bedtime is recommended. Medication therapy is meant to be an adjunct to the other modalities, and its use recommended for an initial period of 4 to 8 weeks. Prolonged therapy with desmopressin has not been studied.[3,4,7,8,10,11]

The most common side effects of intranasal desmopressin are in the nasal mucosa and upper airway passages. These include irritation, conjunctivitis, tinnitus, rhinitis, congestion, sore throat, and epistaxis. These may alter drug absorption as do other conditions such as upper respiratory tract infections and allergic and nonallergic rhinitis. Systemic adverse effects include headache, dizziness, chills, flushing, elevated blood pressure, abdominal pain, and water intoxication. Side effects appear to be dose-related, and temporary cessation of the medication leads to resolution.[7,8,10-12] Drug–drug interaction has not been substantiated.[9,13,14]

The manufacturer also lists several other warnings and precautions in its prescribing literature.[8] Except for hypersensitivity to the drug, there are no absolute contraindications. For very young and elderly patients, adjusting fluid intake is recommended to decrease the potential for water intoxication and hyponatremia. A period of large fluid or water intake just before dosing may lead to a greater volume of water reabsorption. The resulting decrease in osmolality may result in seizures, especially in patients at the extremes of age. Caution is also recommended for patients with conditions related to maintaining fluid and electrolyte balance, such as renal disease, cystic fibrosis, or gastrointestinal diseases, because of the potential for hyponatremia by water intoxication. Likewise, in conditions that may be blood-pressure sensitive, fluid overload may precipitate symptoms of congestive heart failure, coronary artery disease, or hypertrophic cardiomyopathy. For the otherwise healthy patient with primary nocturnal enuresis, the manufacturer recommends checking serum electrolytes once if therapy extends beyond a week, although the exact time for doing so is not clearly stated.[8,9,11]

Potentially the most severe adverse effect with using desmopressin is profound hyponatremia, as presented in our case report patient. Here was an otherwise healthy woman with a progression of symptoms that led to her admission to the hospital for symptomatic hyponatremia. Without knowledge of her desmopressin use, it appeared that the patient's hyponatremia was due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Once the desmopressin use was known, it was clear that her hyponatremia, apparent water intoxication, and resulting presentation were due to the medication.

Literature Review

In reviewing the occurrence of hyponatremia and water intoxication with the use of intranasal desmopressin, a MEDLINE search of the English-language literature from 1966 to the present revealed 13 such case reports. Eleven incidents involved children; two involved adults. While a majority of cases occurred with use of desmopressin for primary nocturnal enuresis, several occurred during use for renal concentration testing and treatment or testing for diabetes insipidus. All patients presented with symptoms of moderate to severe hyponatremia, with serum sodium levels below 123 mmol/L. Convulsions occurred in all but one case. In addition to the use of demopressin, a specific reason for the occurrence of the water intoxication was evident in a majority of the cases. Despite the seriousness of their presentation, recovery was fairly quick, uncomplicated, and complete in all (Table).[9,12,13,15-21]

When examining the details of the cases more closely, two distinct and separate groupings become evident. The larger group included eight cases, in addition to our patient, whose symptoms developed soon after beginning therapy with desmopressin. Several had underlying disease processes that influenced fluid balance, and they also gave a history of excessive fluid intake. Four had a profound response to the first dose of desmopressin. The other patients all were symptomatic by the end of the first week of therapy, and likewise had a history of fluid excess. This was the group that had difficulty in initiating therapy.

In contrast, the smaller group included five patients who had been using desmopressin for a longer period, from 6 weeks upward to years. Their use had been stable until another factor contributed to fluid imbalance. For the one adult, it was 4 L of beer consumption and a self-doubling of the dose of desmopressin. For the children, these ranged from a prolonged bout of diarrhea, to using the bottle to quiet an irritable toddler, to the addition of imipramine and a mild head injury. For one child,

TABLE

Summary of MEDLINE Search (1966-1996) of Case Reports of Hyponatremia Associated with Desmopressin Use

Cited Study (Year)	Age	Sex	Indication	Dose (μg)	Seizures Occur?	Sodium (mmol/L)	Length of Treatment	Findings
Koskimes et al[16] (1984) 3 cases	13 mo	F	RCT	10?	Yes	120	1 d	Onset of symptoms at 11, 15, and 10 hours after dosing; postulated that fluid restriction was not impressed enough on parents.
	1 mo	M	RCT	10	Yes	118	1 d	
	7 mo	F	RCT	10	Yes	123	1 d	
Simmonds et al[18] (1988)	13 y	F	PNE	10/20	Yes	114	4 d	With cystic fibrosis and nasal polyps, on IV antibiotics for *Pseudomonas aeruginosa* respiratory infection; treated for 4 nights with 10, 20, 20, and 10 μg/night; noted sodium was 125 mmol/L after 3rd dose.
Bamford and Cruickshank[19] (1989)	6 y	M	PNE	20	Yes	122	8 d	Extra dosing noted if felt improperly done; excessive daytime fluid intake also noted.
Ferrer et al[20] (1990)	32 y	F	DI	80	Yes	120	1 d	Symptoms 48 hours after receiving dose; psychogenic polydipsia found, and not DI as initially thought.
Salvatoni et al[17] (1990)	15 mo	M	DI	2.5	Yes	111	3 d	Congenital hypothyroid with gluten induced enteropathy and DI. Had a single 10-μg test dose, then therapy for 2 nights.
Beach et al[9] (1992)	10 y	M	PNE	20	Yes	118	3 d	Mother decreased last dose because of good effect; had excess fluid intake for hiccups the day prior. History of microcolon, ileal atresia, and attention deficit; on methylphenidate HCl (Ritalin).
Davis et al[21] (1992)	29 y	M	PNE	80	Yes	118	6+ mo	Self-doubled dose; drank alcohol regularly, with 4 L of beer the night before.
Yaouyanc et al[12] (1992)	28 mo	M	PNE	20	Yes	118	6 wk	Started at 20 μg bid for few days prior and dose changed after emesis; was anorexic, craving salt, having headaches, with more fluid intake by the parents to quiet the crying child.
Hamed et al[13] (1993)	10 y	M	PNE	40	Yes	113	7 mo	Started on imipramine 25 mg; 2 weeks prior with minor head injury. No obvious overhydration known.
Kallio et al[15] (1993) 2 cases	8 y	F	PNE	40	No	120	2+ y	Not complete control even at 40 mg, but had 10 days of diarrhea prior with increased fluid intake. Was unconscious at admission; EEG showed diffuse generalized slowing.
	11 y	M	PNE	20	Yes	123	2 y 1 d	Went drug-free for 2 months before taking 1 dose. Ate and drank normally, with onset of symptoms 2 days later. EEG showed diffuse slowing that persisted at 1 month, and cleared by 7 months. Theorized upregulation with an exaggerated response as the cause.
Present case (1994)	29 y	F	PNE	20	No	123	11 d	Presented 4 days prior with sodium of 127 mmol/L. Hydrated for dehydration and noted salt craving. Patient hydrated to compensate for working outdoors in summer.

NOTE: Dose refers to daily bedtime dose in micrograms, with ? referring to unclear data from the report. Seizures refers to a presentation that included a seizure. Sodium refers to sodium level at admission. Findings includes any concomitant history relating to presentation, causative factors, laboratory data, or dosing pattern.
RCT denotes renal concentration testing; PNE, primary nocturnal enuresis; DI diabetes insipidus.

after 2 years of successful therapy, it was the first dose of desmopressin after a 2-month hiatus. In this group, initial use was without problems or complications, and another factor contributed to the difficulties.

Management

Reviewing these cases brings up some interesting points. One is that none of these cases appeared to be predictable before the onset of symptoms. Another is that the patients and/or parents did not understand or were not informed of the danger of excessive fluid intake with desmopressin. Raising both physician and patient-parent awareness to the problem of severe hyponatremia might help to prevent or minimize its morbidity.

Preventing water intoxication and hyponatremia partly rests with educating the patient and family on the method by which desmopressin works (ie, the temporary reabsorption of water from the kidney). Prolonged desmopressin action, overall excessive fluid intake, and too much fluid intake near the dosing time are all factors that result in more water reabsorption than anticipated. This leads to electrolyte dilution that will have a wide variety of symptoms related to the degree of hyponatremia or the amount of acute change. Preventing this complication from occurring also rests with educating the patient and family on the symptoms of mild hyponatremia before a patient develops seizures or altered mentation. Initial symptoms are often vague and nonspecific. More noticeable symptoms do not present until sodium levels fall below 125 mmol/L, unless the decrease is abrupt. Patient and parents should be warned that other conditions may make fluid and electrolyte balance more tenuous, such as fever, viral illnesses, endocrine disorders, trauma, cystic fibrosis, renal disease, and gastrointestinal illnesses.

Prolonged therapy has not been fully studied. Patients are felt to experience a downregulation of receptor sites after prolonged use and an upregulation of receptor sites after cessation of use. Tolerance develops in some, and these patients may have an overexaggerated response after taking no desmopressin for a prolonged period.[8,15] For others, though, a lower dose may be just as therapeutic without side effect or loss of effect. Electrolyte studies may be helpful for any vague, nonspecific complaints (even if sooner than recommended), especially when concomitant illness may alter fluid or electrolyte balance. Periodic laboratory studies may also provide reassurance in cases of prolonged therapy extending beyond the initial 8-week period, when changing the dosing regimen, or when reintroducing the medicine after a prolonged break in therapy.

Finally, it is essential to provide continual follow-up after starting therapy. Primary nocturnal enuresis is a complex problem with psychological factors along with physical symptoms. Therapy entails a multitude of treatment approaches. Continual follow-up not only establishes better rapport, trust, and comfort, but also will allow for better monitoring of the physical symptoms and, it is hoped, earlier detection of iatrogenic side effects. As initial success with desmopressin is obtained, other approaches may or may not be reintroduced; medication use may be reduced, eliminated, or continued indefinitely. Treatment of this condition involves a long relationship between practitioner and the patient. Chronicity and continuity of care will ultimately lower the risk of complications and provide more fulfilling therapy for all.

Conclusions

Desmopressin is an effective medication for nocturnal enuresis, for both adults and children. Like all drugs, though, it is not without side effects and complications. The most likely life-threatening complications are water intoxication and hyponatremia. The best management tools for minimizing these complications are prevention and early recognition. Adjusting the dosage to the lowest needed may minimize side effects. Providing patients and their families with a good, simple understanding of how desmopressin works and how they may minimize problems is essential. Following the patient long term may allow for early detection before a serious problem arises. Likewise, periodic electrolyte monitoring, especially in times of concomitant illness, change in therapy, or reintroduction of therapy, may detect early cases of hyponatremia. Furthermore, desmopressin use should be considered in the differential diagnosis for patients presenting with hyponatremia and a history of primary nocturnal enuresis. As its use becomes more routine, it is imperative that physicians become aware not only of its benefits, but also of its potentially harmful side effects.

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