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# Hyponatremia in patients with nocturnal enuresis treated with DDAVP

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**Abstract** Treatment of nocturnal enuresis with DDAVP is associated with a low incidence of adverse effects. The only reported serious adverse effect is seizure or altered level of consciousness due to water intoxication. We reviewed 14 articles that reported data on serum sodium in patients treated with DDAVP for nocturnal enuresis and 11 articles that reported patients who developed a seizure or altered level of consciousness during treatment with DDAVP for nocturnal enuresis. Excess fluid intake was identified as a contributing factor in 6 of the 11 case reports.

**Conclusion** Hyponatremia is a potential adverse effect in patients with nocturnal enuresis who are treated with DDAVP. To prevent this adverse effect, we recommend that the patients prescribed DDAVP for nocturnal enuresis should be counseled not to ingest more than 240 ml (8 ounces) of fluid on any night that DDAVP is administered.

**Key words** Nocturnal enuresis · DDAVP · Hyponatremia · Water intoxication

**Abbreviation** *AVP* arginine vasopressin

## Introduction

DDAVP effectively controls nocturnal enuresis in over 50% of patients with this problem [22, 31]. DDAVP's precise mechanism of action in the control of nocturnal enuresis is not understood. DDAVP, a synthetic analog of arginine vasopressin (AVP), was developed by removing an amino group in position 1 and substituting L-arginine in position 8 with D-arginine, which resulted in selective V2 agonist (antidiuretic) properties. The onset and maximal pharmacologic action of intranasally administered DDAVP occurs within 60 min, and the duration of peak drug levels and maximum pharmacologic action is about 4 h [8]. Treatment of nocturnal enuresis with DDAVP is associated with a low incidence of adverse effects [9, 23, 24]. The only reported serious adverse effect is seizure or altered level of consciousness resulting from water intoxication. We reviewed the medical literature on the treatment of nocturnal enuresis with DDAVP to determine if factors could be identified that might increase the incidence of this serious adverse effect.

## Methods

A Medline search of the English language literature between the years 1966 and 1994 was conducted to identify articles published on the treatment of nocturnal enuresis with DDAVP. The reference section of each article was reviewed to identify other articles not listed in Medline. We reviewed all the articles to identify studies that reported data on the serum sodium during treatment with DDAVP and case reports of seizure or altered level of consciousness due to water intoxication in patients treated with DDAVP. The studies that reported data on serum sodium were specifically re-

**Table 1** Data on case reports of seizure or altered level of consciousness due to water intoxication in patients treated with DDAVP. *H* headache, *N* nausea, *V* vomiting, *S* seizure, *D* disoriented, *R* Ritalin, *T* Tofranil

| Author | Age (year) | Sex | Dosage (μg) | Duration on DDAVP | Time of symptoms | Symptoms | $Na^+$ mmol/l | Excess fluids | CNS drug |
|---|---|---|---|---|---|---|---|---|---|
| Simmonds et al. 1988 [26] | 13 | F | 10–20 | 4 days | | H, N, V, S | 114 | + | |
| Bamford and Cruickshank 1989 [1] | 6.5 | M | 20 | 8 days | 11.00 a.m. | H, V, S | 122 | + | |
| Blanchard and Brossier 1991 [3] | 5 | M | 20 | 5 weeks | | S | 117 | | |
| Beach et al. 1992 [2] | 10 | M | 10–20 | 4 days | a.m. | V, S | 118 | + | R |
| Davis et al. 1992 [4] | 29 | M | 80 | | | S | 118 | + | |
| Muglia et al. 1992 [19] | 15 | M | 10–20 | 7 months | 4.00 a.m. | H, D | 124 | – | |
| Yaouyanc et al. 1992 [32] | 2 | M | 20 b.i.d. | 6 weeks | | H, V, S | 118 | + | |
| Hamed et al. 1993 [7] | 10 | M | 20–40 | 7 months | 4.00 p.m. | S | 113 | – | T |
| Hourthane and Salisbury 1993 [11] | 8 | F | 20 | 2 days | 12 h. | S | 119 | – | |
| Kallio et al. 1993 [13] | 8 | F | 40 | 2 years | | D | 120 | + | |
| Kallio et al. 1993 [13] | 12 | M | 20 | 2 years | | H, V, S | 123 | – | |

viewed for the number of patients studied, whether the patients were screened to identify those patients with a low nocturnal secretion of AVP, design of the study, dosage of DDAVP, duration of treatment prior to obtaining the serum sodium, time of day the serum sodium was obtained, and serum sodium data during treatment with DDAVP. The case reports of seizure or altered level of consciousness were specifically reviewed for the age and sex of the patient, significant pre-existing illness, dosage of DDAVP, symptoms of water intoxication, duration of time on DDAVP prior to developing symptoms, time of day the symptoms developed, admission serum sodium, whether the patient had ingested a large amount of fluid during the day preceding the symptoms, whether the patient was on any other medication, and the outcome. A normal serum sodium concentration was considered to be 135–145 mmol/l.

## Results

Fourteen articles were identified that reported data on serum sodium in patients during treatment with DDAVP [6, 10, 12, 14–16, 18, 20, 21, 25, 27–30]. A total of 529 patients were included in these articles.

Only one of the studies reported data exclusively on patients with a low nocturnal secretion of AVP [27]. Steffens et al. [27] reported no difference in the serum sodium in 14 patients with a low nocturnal secretion of AVP who were treated with DDAVP.

The study designs varied from double-blind cross-over trials to uncontrolled reports of clinical experience with the use of DDAVP. The dosage of DDAVP in the studies varied from 5 to 40 μg delivered intranasally or 200–400 μg administered orally. None of the studies reported any data on whether the serum sodium varied with the dosage of DDAVP. The specific duration of time on DDAVP prior to assessing the serum sodium concentration was reported in only six of the articles [6, 10, 14, 18, 20, 27]. The serum sodium was measured weekly in two studies, and after 1 day, 3 days, 2, 4, and 8 weeks, and 1 month, respectively, in the other studies [6, 10, 14, 18, 20, 27]. The time of day the serum sodium was measured was reported in only four studies [6, 14, 21, 27]. In these studies, the serum sodium was measured at 5:00 a.m., 8:00 a.m., „morning," and „night," respectively [6, 14, 21, 27].

Ten of the articles did not report specific data on the serum sodium but reported the serum sodium or serum electrolytes were normal, no differences in the serum sodium or electrolytes, or no adverse effects [12, 15, 18, 21, 25, 28–30]. Of the four articles that reported specific data on the serum sodium, three reported asymptomatic hyponatremia. Fjellestad-Paulsen et al. [6] reported that 3 (10%) of 30 patients developed hyponatremia, defined as a serum sodium between 125 and 130 mmol/l. Key et al. [14] reported the range of serum sodium in 59 patients was 130–140 mmol/l with a mean of 138 mmol/l. It is not clear how many of the patients had a serum sodium less than 135 mmol/l [14]. Matthiesen et al. [16] reported 1 (3%) of 33 patients had a serum sodium of 128 mmol/l. Since the serum sodium measured before and after this value was normal, the authors concluded the result was likely erroneous [16]. One other study reported specific data on the serum sodium [20]. Ramsden et al. [20] reported a double-blind cross-over trial in 21 patients. The serum sodium while on placebo was 139.9 mmol/l compared to 139.6 mmol/l while on DDAVP [20]. None of the patients in the studies developed seizure or altered level of consciousness [6, 10, 12, 14–16, 18, 20, 21, 25, 27–30].

We identified 11 case reports of seizure or altered level of consciousness due to water intoxication [1–4, 7, 11, 13, 19, 26, 32]. Data obtained from these case reports are shown in Table 1.

## Discussion

It is estimated that over 250,000 patients in the United States have been treated with DDAVP since the nasal

spray preparation was introduced in 1989. Treatment with DDAVP has improved the quality of life of thousands of patients with nocturnal enuresis. Adverse effects due to treatment with DDAVP are uncommon [9, 23, 24]. The only serious adverse effect is seizure or altered level of consciousness due to water intoxication.

Based on the limited data available in the studies we reviewed, mild, asymptomatic hyponatremia might develop in 1%–10% percent of patients treated with DDAVP for nocturnal enuresis [6, 16]. The precise incidence of hyponatremia is not known since none of the studies reported data on the serum sodium concentration during the period of maximal pharmacologic action of DDAVP.

Since seizure or altered level of consciousness due to the water intoxication are uncommon, it is likely that factors other than the presence of pharmacologically active amounts of DDAVP are necessary for this adverse effect.

Excess fluid intake was identified as a contributing factor in 6 of the 11 case reports [1, 2, 4, 13, 26, 32]. Evening fluid restriction is a common practice in most patients with nocturnal enuresis before they seek medical attention. Consequently, most patients with nocturnal enuresis who are treated with DDAVP do not ingest a large quantity of fluid during the evening. This might account for the uncommon reports of symptoms due to water intoxication. However, some authors suggest evening polydipsia might be more common in patients with nocturnal enuresis than is generally appreciated [5, 17, 25]. In the six case reports where ingestion of a large amount of fluid was considered to be a contributing factor, the circumstances leading to fluid ingestion included intravenous therapy, beer drinking, habitual ingestion, and treatment of hiccups, diarrhea, and crying [1, 2, 4, 13, 26, 32]. Beach et al. [2] calculated the serum sodium should not fall greater than 5–7 mmol/l if a patient treated with DDAVP does not ingest greater than 30 ml of fluid per kg body weight during the 4 h prior to a dose of DDAVP and for 12 h after the dose [2].

One patient who developed a seizure had cystic fibrosis [26]. The authors speculated the abnormal electrolyte transport in patients with cystic fibrosis might increase the risk of symptomatic hyponatremia. The patient was receiving intravenous fluid therapy for several days prior to developing symptoms, so an increased fluid intake might also be a risk factor [26].

Higher doses of DDAVP prolong the duration of pharmacologic action and might increase the risk of water intoxication [8]. None of the studies that reported data on the serum sodium during treatment with DDAVP assessed the incidence of hyponatremia with different dosages of DDAVP. Seizure or altered level of consciousness developed in patients taking conventional dosages of DDAVP ranging from 10 to 40 μg. The only patient who developed seizures with a larger than conventional dosage (80 μg) also ingested at least 4 l of beer the night before the seizure, making excess fluid intake a likely factor in the water intoxication [4]. Some authors suggest the ingestion of larger-than-prescribed amounts of DDAVP might be more common than is appreciated [9]. These authors speculate that some patients who are not completely dry on the prescribed dose might increase the dose in an attempt to improve efficacy [9]. Only one study reported data on the serum sodium in treated patients who were previously identified as having a low nocturnal secretion of AVP [27]. The effect of the pharmacologic action of DDAVP in addition to naturally occurring AVP in patients with a normal nocturnal increase in AVP might increase the V2 agonist effect and the risk of water intoxication.

Nine of the 11 patients developed a seizure and two patients became disoriented but did not develop a seizure [1–4, 7, 11, 13, 19, 26, 32]. Six of the 11 patients had other symptoms preceding the seizure or altered level of consciousness [1, 2, 13, 19, 26, 32]. Five patients had headache, five vomited, and one had nausea [1, 2, 13, 19, 26, 32]. Previous studies of adverse effects in patients with nocturnal enuresis treated with DDAVP report headache in 0.4%–1.3% of patients [9, 24]. It is possible the headaches in these patients might have represented transient episodes of symptomatic water intoxication.

Two of the patients who had seizure or altered level of consciousness were also taking a neurologically active medication at the same time as the DDAVP [2, 7]. One patient had been on methylphenidate for 2 years and developed a seizure 4 days after starting DDAVP [2]. The seizure developed after the ingestion of a large quantity of fluid in the preceding day [2]. Another patient developed a seizure after taking DDAVP for 7 months, the latter 3 months of which the patient was also taking imipramine [7]. There was no history of excess fluid intake in this patient [7]. Both methylphenidate and imipramine are neurologically active medications, and it is possible that these medications could act to potentiate the action of DDAVP [2, 7].

Kallio et al. [13] reported a 12-year-old who was treated with DDAVP for 2 years. The DDAVP was discontinued for 2 months and then restarted at the same dose. The patient had a seizure after the first dose. There was no history of ingestion of a large amount of fluid before the seizure. The authors speculated the V2 receptors in the kidney had been „up-regulated" and were therefore more sensitive to the action of the DDAVP [13].

Neurological symptoms developed in the first 10 days after the start of treatment in 4 of the 11 patients and 5 weeks–2 years after the start of treatment in the remaining 7 patients [1–4, 7, 11, 13, 19, 26, 32]. The wide variability in the onset of neurological symptoms makes hypersensitivity to DDAVP a less likely reason to account for the water intoxication.

All of the patients who developed neurological symptoms recovered [1–4, 7, 11, 13, 19, 26, 32]. A CT of the brain was performed in seven patients and was normal in each case [1, 2, 4, 11, 19, 26]. Limited follow-up data

were reported in five of the case reports [1, 7, 13, 26]. The duration of follow-up ranged from 2 weeks to 7 months. The patients were reported to be normal at follow-up [1, 7, 16, 32].

Like all medications, DDAVP has potential adverse effects. Water intoxication is an uncommon but serious potential adverse effect of treatment with DDAVP in patients with nocturnal enuresis. Patients should fill out a micturition diary, which should exclude polydipsia before antidiuretic treatment is given. DDAVP should only be prescribed with specific instructions regarding the risks associated with excess ingestion of fluid. The risk of seizure or altered level of consciousness can be minimized by specific counseling of patients not to drink a large quantity of fluid on any evening DDAVP is administered. We recommend patients who take DDAVP not drink greater than 240 ml (8 oz) of fluid on any evening DDAVP is administered. Patients should be specifically counseled not to take a larger dose than prescribed. If a patient who is taking DDAVP develops headache, nausea, or vomiting, the DDAVP should be discontinued and the patient should promptly notify the physician. With this approach, supported by a recent study confirming the safety of DDAVP, we feel that treatment with DDAVP is safe [9].

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