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# Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series

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## ABSTRACT

**Background.** Desmopressin (DDAVP) is typically prescribed for central diabetes insipidus, von Willebrands disease and for enuresis. DDAVP-associated hyponatremia is a known complication of DDAVP therapy. The currently recommended treatment for this condition calls for discontinuing DDAVP as part of the initial therapy. This recommendation could lead to a water diuresis and potentially over-correction of the serum sodium.

**Methods.** The 15 patients in this case series developed symptomatic DDAVP-associated hyponatremia and were admitted to acute care hospitals. Thirty-eight percent presented with symptomatic hyponatremia and 62% developed symptomatic hyponatremia due to concomitant DDAVP and hypotonic intravenous fluid administration during a hospital stay. Group 1 patients ( $n = 13$ ) were treated by withholding DDAVP and providing intravenous saline. Group 2 patients ( $n = 2$ ) were treated by continuing DDAVP and providing DDAVP and intravenous hypertonic saline.

**Results.** Among Group 1 patients, in whom DDAVP was withheld as initial management of DDAVP-associated hyponatremia ( $n = 13$ ), the mean change in serum sodium in the first 2 days of treatment was  $37.1 \pm 8.1$  mEq/L. The ultimate outcome in this group was death in 23%, severe brain damage in 69% and moderate brain damage in 8%. In Group 2 patients, in whom DDAVP was continued ( $n = 2$ ) as part of the initial management strategy, the mean change in serum sodium was  $11.0 \pm 0$  mEq/L in the first 2 days. The ultimate outcome was survival without neurological sequelae in both cases.

**Conclusions.** Discontinuing DDAVP in a patient with symptomatic DDAVP-associated hyponatremia can lead to rapid correction of the serum sodium and resultant severe neurological injury. In contrast, continuing the medication while correcting DDAVP-associated hyponatremia may lead to better outcomes by avoiding over-correction of the serum

sodium. Thus, an alternative approach that we propose is to continue DDAVP as part of the initial management of this disorder.

**Keywords:** central pontine myelinolysis, DDAVP, desmopressin, hyponatremia

## INTRODUCTION

Desmopressin (1-deamino-8-D-arginine vasopressin, a.k.a. DDAVP), a synthetic vasopressin receptor agonist, is typically prescribed for central diabetes insipidus, von Willebrands disease and for enuresis in children and the elderly. DDAVP-associated hyponatremia is a known complication of DDAVP therapy and is not an uncommon clinical encounter [1]. The expansion of DDAVP use for causes unrelated to central diabetes insipidus and the ease of administration of intranasal preparations have been two factors that have led to the increasing use of this medication. When use of DDAVP leads to severe, symptomatic hyponatremia with neurological symptoms, the clinician faces a challenging clinical dilemma. On the one hand, acutely raising the serum sodium with hypertonic saline is indicated; however, if the DDAVP is simply withheld, a spontaneous free water diuresis will occur as the urine osmolality drops and auto-correction of the serum sodium can occur. Therefore, if intravenous saline is administered and DDAVP is withheld at the same time, the potential for rapid changes in serum sodium exists. This combination of factors can lead to overly rapid correction of the serum sodium which puts the patient at risk for severe neurological injury. Very little is written about how to handle this situation as leading clinical references are silent on this topic [2, 3]. In fact, a recent position paper by the European Society of Critical Care failed to give any information about the condition of DDAVP-associated hyponatremia [4]; therefore, there is nothing in the literature to address this point to date. It is common clinical practice to withhold any medication that

causes toxicity, and this advice is echoed by Micromedex®, which suggests holding DDAVP if hyponatremia occurs; however, no suggestions regarding fluid therapy are given [3]. Previous case reports suggest that discontinuing DDAVP and giving hypertonic saline when treating DDAVP-associated hyponatremia can put patients at risk of overly rapid correction of the serum sodium and iatrogenic neurological injury and possibly patient death [5, 6]. A recent report has suggested that adding DDAVP when a water diuresis ensues has been suggested as a strategy for avoiding overly rapid correction of the serum sodium [7]. In this study we investigate how either discontinuing or continuing DDAVP can influence the rate of correction of serum sodium and the potential for resultant neurological injury.

## MATERIALS AND METHODS

Fifteen cases were studied (Tables 1 and 2). All patients were admitted to acute care hospitals in both academic and community-based settings (Figure 1). The average age of the patients was 37 years (ranging from 13 to 71 years). The patients were mostly (73%) female. The indication for the use of DDAVP was central diabetes insipidus (73%), Von Willebrand's disease (20%) and enuresis (7%). The majority (66%) of the patients had been taking DDAVP chronically prior to presentation, the others started DDAVP for a surgical procedure due to Von Willebrand's disease or for newly developed diabetes insipidus. The 15 cases occurred over a period of 5 years from 13 hospitals, throughout the USA in both academic and community medical center settings. In Group 1, one of the authors (J.C.A.) was consulted on these cases after neurological injury had occurred in order to determine the reason for brain damage or death and whether the treatment provided was the cause of this. The cases were referred from hospital risk management committees. In Group 2, one of the authors was involved in the care of the patients. This case series study was approved by the Institutional Review Board at Lakeland Regional Center, Lakeland, FL.

## RESULTS

### Group 1 (cases where DDAVP had been discontinued upon recognition of DDAVP-associated hyponatremia)

All patients had developed clinically significant hyponatremia, 38% presented with symptomatic hyponatremia and 62% developed symptomatic hyponatremia due to concomitant DDAVP and hypotonic intravenous fluid administration. In five of these cases the patients were taking DDAVP chronically and they presented to the hospital with hyponatremia. Eight cases involved the administration of hypotonic (77 mmol/L NaCl) fluids or failure to fluid restrict a patient receiving DDAVP and subsequent hyponatremic encephalopathy developed (Figure 1). Mean fluid intake for patients who developed hyponatremia in hospital ( $5.8 \pm 0.7$  L) and urine output was  $1.3 \pm 0.2$  L. This led to mean fluid balance of positive  $4.5 \pm 0.3$  L. This occurred  $45 \pm 8$  h after start of IV fluid therapy and

DDAVP. Obviously, these figures are not known for those who presented with hyponatremia. Upon recognition of hyponatremic encephalopathy, DDAVP was discontinued in these cases. In 92% of the cases hypertonic saline was used for correction of hyponatremia and in 8% isotonic saline was administered (Table 1). The mean dose of 3% saline in Group 1 was  $341.4 \pm 57.8$  mL. All patients upon discontinuation of DDAVP underwent increase in urine output to over 200 cc per hour. The mean change in serum sodium in the first 2 days following the recognition of DDAVP-associated hyponatremia was  $37.1 \pm 8.1$  mEq/L. The ultimate outcome was death in 23%, severe brain damage (severe cognitive impairment to a vegetative state) in 69% and moderate brain damage (cognitive impairment) in 8%. Eleven cases underwent neurological imaging that showed extensive demyelinating lesions both pontine and extrapontine. Three deaths, all of which were due to brain injury, occurred in the cohort, and all occurred within 45 days of the diagnosis of hyponatremia. Of one patient that died with autopsy performed, diffuse demyelinating lesions were seen involving the cerebral cortex, basal ganglia and cerebral infarcts.

### Group 2 (cases where DDAVP was continued upon recognition of DDAVP-associated hyponatremia)

One case involved a nursing home patient given DDAVP chronically for enuresis and one case involved a patient with central diabetes insipidus who developed hyponatremic encephalopathy following administration of hypotonic fluids and DDAVP. In both of these cases DDAVP was continued (intranasal) and 3% sodium chloride was administered intravenously (Table 2). The mean dose of 3% saline given in Group 2 was 440 mL. There was no significant difference between Groups 1 and 2 ( $P = 0.09$ ). DDAVP was provided at the usual maintenance dose for each patient (through intranasal route in one case and orally in the other). Serum sodium was checked every 4 h during the infusion of hypertonic saline (Figure 2). The change in serum sodium in the first 2 days following the recognition of DDAVP-associated hyponatremia was  $11.0 \pm 0$  mEq/L ( $P < 0.001$ ) in both of these cases. Both patients survived without neurological sequelae. In one case brain magnetic resonance imaging was obtained 6 months later for unrelated reasons (evaluation of headache) and no evidence of pontine myelinolysis was found. In both of these cases no increase in urine output was noted during the correction of hyponatremia with hypertonic saline consistent with a continued anti-diuretic state.

## DISCUSSION

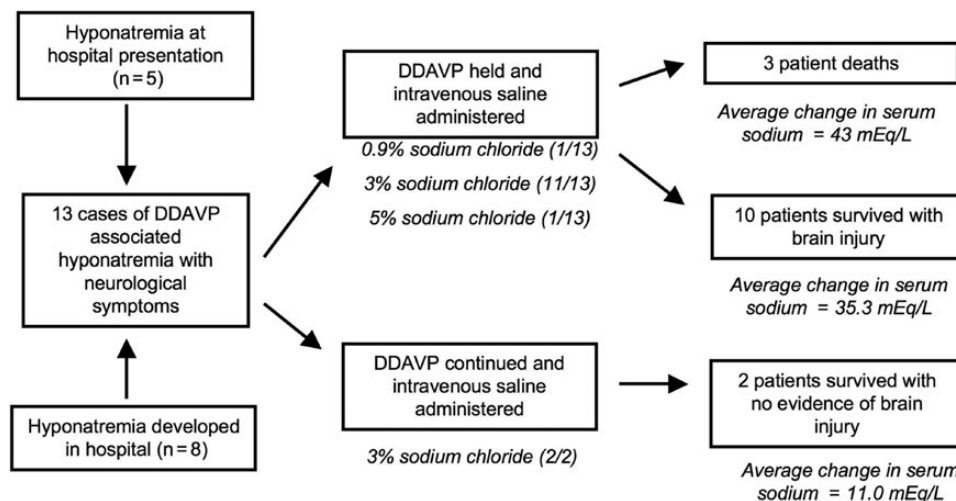
The present study describes the treatment of 15 patients with symptomatic DDAVP-associated hyponatremia and their subsequent care. Thirteen patients (Group 1) were treated by stopping the medication and given intravenous saline (mostly hypertonic saline) and this group of patients developed overly rapid correction of the serum sodium (37 mEq/L in the first 48 h) and severe neurological injury. Two patients (Group 2) were treated by continuing the DDAVP to prevent auto-correction of the serum sodium and were given intravenous

Table 1. Group 1 patients, DDAVP withheld during management of hyponatremia

Diagnosis	Age/ gender	Serum sodium			Development of hyponatremia	Clinical presentation	Treatment	Neuroimaging	Outcome
		Initial	At start of treatment	After 48 h of treatment					
Von Willebrands disease	31/F	143	108	142	Received hypotonic fluids and DDAVP	Headache, nausea, lethargy	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	28/F	138	108	141	Received hypotonic fluids and DDAVP	Headache, nausea, lethargy	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Von Willebrands disease	32/F	138	108	141	Received hypotonic fluids and DDAVP	Seizures, coma	5% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	18/M	117	115	144	As initial presentation	Seizures, coma	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	59/F	119	110	143	As initial presentation	Seizures, coma	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Cognitive impairment
Central diabetes insipidus	37/F	116	101	150	As initial presentation	Seizures, coma	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Death
Central diabetes insipidus	35/F	142	121	168	Received hypotonic fluids and DDAVP	Seizures, coma	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	56/F	114	114	147	As initial presentation	Dizziness, vomiting	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Von Willebrands disease	22/M	140	115	144	Received hypotonic fluids and DDAVP	Dizziness, vomiting	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	28/F	136	105	136	Received hypotonic fluids and DDAVP	Headache, vomiting, respiratory arrest	0.9% NaCl + holding DDAVP	Not available	Death
Central diabetes insipidus	13/F	136	120	169	Received hypotonic fluids and DDAVP	Hallucinations, seizure, respiratory arrest	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	26/F	140	108	141	Received hypotonic fluids and DDAVP	Seizures	3% NaCl + holding DDAVP	Extrapontine and pontine demyelination	Severe brain damage
Central diabetes insipidus	37 /F	118	101	150	As initial presentation	Confusion, emesis, respiratory arrest	3% NaCl + holding DDAVP	Not available	Death
Mean ± SD	32.5/85% F	129.2 ± 13.8	110.3 ± 6.4	147 ± 10.1					

**Table 2. Group 2 patients, DDAVP continued during management of hyponatremia**

Diagnosis	Age/ gender	Serum sodium			Development of hyponatremia	Clinical presentation	Treatment	Neuroimaging	Outcome
		Initial	At start of treatment	After 48 h of treatment					
Enuresis	73/M	117	117	128	DDAVP as an outpatient	Ataxia, nausea, obtundation	3% NaCl + continue DDAVP	Normal	Recovery without neurological damage
Central diabetes insipidus	61/M	138	116	127	Received hypotonic fluids and DDAVP	Headache, nausea, confusion	3% NaCl + continue DDAVP	None	Recovery without neurological damage
Mean	67 ± 6/ 100% M	127.5 ± 10.5	116.5 ± 0.5	127.5 ± 0.5					



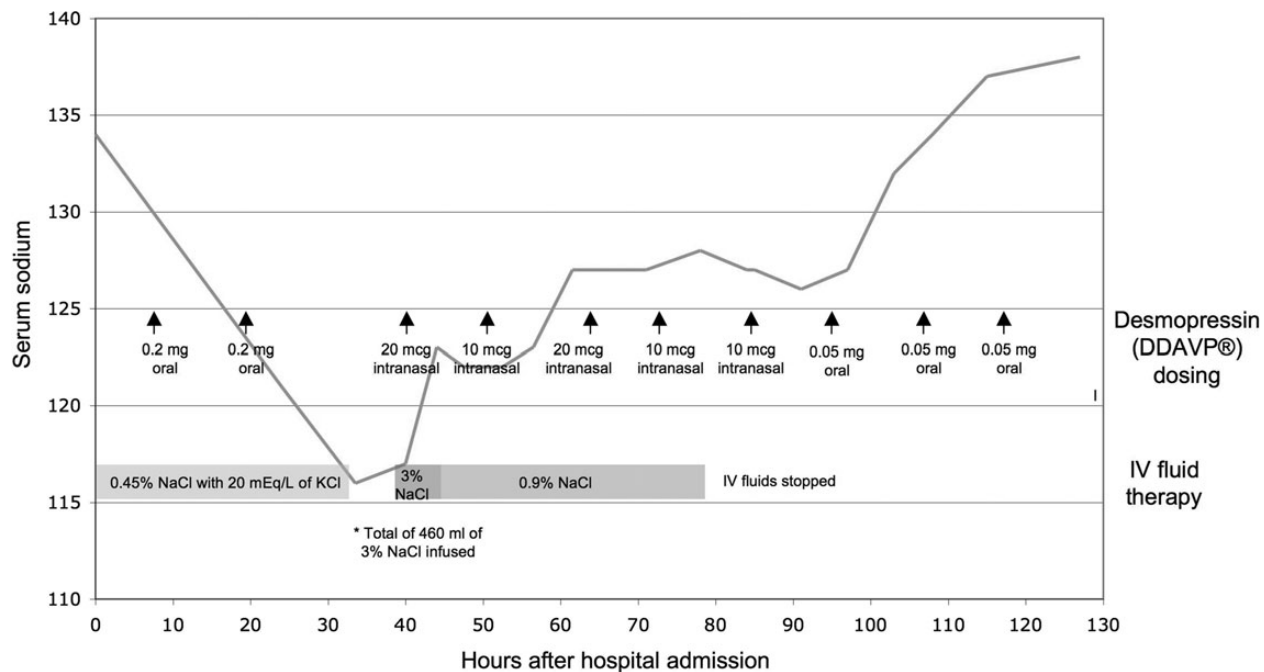
**FIGURE 1: Patient treatment and outcome.**

hypertonic saline and the serum sodium corrected at an appropriate rate (11 mEq/L *n* the first 48 h) and these patients suffered no neurological sequelae. These findings suggest that discontinuing DDAVP and administering intravenous saline in a patient with symptomatic DDAVP-associated hyponatremia can lead to rapid correction of the serum sodium and resultant severe neurological injury. This series also points out the dangers involved with administration of DDAVP along with hypotonic intravenous fluids since many of the patients in Group 1 developed hyponatremia as a consequence of inappropriate prescription of DDAVP concurrent with hypotonic intravenous fluids. This combination is almost never appropriate, and under most circumstances the use of DDAVP and hypotonic fluids should be considered contra-indicated.

Recall that water balance is achieved through regulation of ADH secretion from the hypothalamus through the action of osmoreceptors in the neurohypophysis in which ADH secretion is suppressed during times of plasma hypotonicity and whose secretion is up-regulated as plasma tonicity increases. In the absence of ADH activity, water reabsorption from the urine across the medullary concentration gradient is not permitted and very dilute urine is excreted. When DDAVP is taken, urinary concentration is high and very little free water is

excreted. Excessive water intake or administration of hypotonic fluids to a patient taking DDAVP can therefore lead to a reduction in the serum sodium, and ultimately if the situation is not corrected symptomatic hyponatremia may ensue. Hyponatremic encephalopathy, the clinical manifestations of cerebral edema secondary to hyponatremia, can have a wide range of presentations. The early signs are usually non-specific: nausea, vomiting, headaches (hyponatremic encephalopathy) [8]. Worsening of brain swelling then leads to decreased mental status and seizures; the final manifestations are coma, respiratory arrest and death [8, 9].

The management of a patient with DDAVP-associated hyponatremia poses particular difficulties. This is because a patient with DDAVP-associated hyponatremia is initially in an anti-diuretic state and the acutely symptomatic patient will need early treatment to bring up the serum sodium with hypertonic saline to prevent the complications of cerebral edema. However, if the DDAVP is discontinued, a state of water diuresis may occur where urinary dilution is now maximal and the patient will excrete copious amounts of free water. This can put the patient at risk of auto-correction of the serum sodium and significant auto-correction can occur, especially if intravenous saline is given at the time (as was seen in



**FIGURE 2:** Detailed IV fluid administration, DDAVP dosing and serum sodium levels for a representative case from Group 2. This patient was taking DDAVP chronically for central diabetes insipidus and developed hyponatremia due to concurrent administration of DDAVP and hypotonic fluids following elective surgery.

this case series among Group 1 patients where the serum sodium corrected by 37 mEq/L over 48 h). Our group in 1993 advanced the hypothesis that DDAVP could be used to curtail the significant water excretion during correction of hyponatremia in cases that involve a risk of water diuresis during correction of hyponatremia such as compulsive water drinking, cortisol deficiency, thyroid deficiency and medication-induced hyponatremia (for example thiazide diuretics) [10]. This concept has been validated in a later paper showing the clinical utility of this therapeutic maneuver [11]. The present manuscript demonstrates that DDAVP-associated hyponatremia should be added to the causes of medication-induced hyponatremia in which a reversible impairment of water excretion can occur, which may result in a significant water diuresis.

When dealing with a medication-induced toxicity, it is common clinical logic to withhold the offending agent as the first step and often the mainstay of management and this is the current recommended approach in dealing with DDAVP-associated hyponatremia [2, 3]. However, we are proposing that in the proper clinical circumstance, this can lead to serious neurological injury and death as this case series demonstrates. This is because the impairment of free water excretion that led to the hyponatremia is transitory, and once the medication is stopped, free water excretion can occur unabated. This spontaneous water diuresis, especially if the serum sodium has already been corrected with hypertonic saline, can lead to severe overly rapid correction of hyponatremia to very dangerous levels as we have shown. Of further concern, if the patient has central diabetes insipidus and DDAVP is withheld, over-correction past the point of normonatremia can occur and this is a further risk factor for cerebral demyelination [12]. Therefore in the management of DDAVP-

associated hyponatremia with neurological symptoms, the drug should not be withheld and the medication should be continued, despite the presence of hyponatremia. Symptomatic individuals should be treated with hypertonic saline while continuing DDAVP, a 100 cc bolus of 3% saline can be used as initial therapy (Figure 3) [13]. If this bolus approach is used acutely in the symptomatic individual, the serum sodium should be checked within the first few hours of treatment to be certain that the change in serum sodium achieved is sufficient to treat underlying cerebral edema. It is worth mentioning that there is a theoretical disadvantage to continuing DDAVP in the early phase of treatment and that would be that if hypertonic fluid is not administered quickly to the symptomatic patient, then continuing DDAVP would curb any 'auto-correction' that may occur due to withholding DDAVP. It is important not to delay hypertonic fluid therapy if DDAVP is continued in the patient with symptomatic DDAVP-induced hyponatremia.

Our data have some very important limitations that restrict the conclusions that can be drawn and affect the generalizability of our findings. Firstly, the source of the cases being referral based upon poor outcome skews findings towards the poor outcomes we report in many of these cases. We certainly do not know how often the holding DDAVP approach leads to brain injury. Secondly, we do not have any insight into the epidemiology of this problem since our data do not allow one to know the incidence of this complication. We take the utmost caution in interpreting the differences in outcome between Group 1 and Group 2 in this case series. It is obvious that there are vast differences between the groups and the differences in outcome cannot be attributed solely to the differences in fluid management style. We present these cases as an

## Proposed Treatment of DDAVP Associated Hyponatremia

Symptomatic (seizures, respiratory failure, altered sensorium, vomiting, headache) DDAVP associated hyponatremia



- 1) Continue DDAVP
- 2) Restrict fluid intake
- 3) Start with 100 cc bolus of 3% saline if life threatening cerebral edema is present (e.g. intractable seizures, respiratory failure). May repeat until clinical response achieved while not correcting sodium more than 5 mEq/L in initial period. Serum sodium should be checked following initial bolus to assess adequate response.
- 4) Final correction of serum sodium should not exceed more than 15-20 mEq/L in first 48 hours.

**FIGURE 3:** Proposed treatment protocol for symptomatic DDAVP-associated hyponatremia.

alternative strategy alone, not to suggest that a direct comparison between these groups is possible.

In summary, with the limitations of this case series in mind, clinicians need to be very mindful of this entity because prompt recognition of DDAVP-associated hyponatremia is critical since rapid changes in clinical course with potentially disastrous consequences can ensue if the entity is not treated appropriately. We feel that DDAVP should not be stopped as part of the initial management of this disorder in order to prevent over-correction of the serum sodium and possible neurological injury. We feel that continuing DDAVP and providing hypertonic saline rather than discontinuing the drug be considered as part of the initial management of this disorder in order to prevent over-correction of the serum sodium and possible neurological injury.

## CONFLICT OF INTEREST STATEMENT

None declared.

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