CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Desmopressin to Prevent Rapid Sodium Correction in Severe Hyponatremia: A Systematic Review

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ABSTRACT

BACKGROUND: Hyponatremia is common among inpatients and is associated with severe adverse outcomes such as osmotic demyelination syndrome. Current guidelines recommend serum sodium concentration correction targets of no more than 8 mEq/L per day in patients at high risk of osmotic demyelination syndrome. Desmopressin is recommended to control high rates of serum sodium concentration correction in severe hyponatremia. However, recommendations are based on limited data. The objective of this study is to review current strategies for DDAVP use in severe hyponatremia.

METHODS: Systematic literature search of 4 databases of peer-reviewed studies was performed and study quality was appraised.

RESULTS: The literature search identified 17 observational studies with 80 patients. We found 3 strategies for desmopressin administration in hyponatremia: 1) proactive, where desmopressin is administered early based on initial serum sodium concentration; 2) reactive, where desmopressin is administered based on changes in serum sodium concentration or urine output; 3) rescue, where desmopressin is administered after serum sodium correction targets are exceeded or when osmotic demyelination appears imminent. A proactive strategy of desmopressin administration with hypertonic saline was associated with lower incidence of exceeding serum sodium concentration correction targets, although this evidence is derived from a small case series.

CONCLUSIONS: Three distinct strategies for desmopressin administration are described in the literature. Limitations in study design and sample size prevent definitive conclusions about the optimal strategy for desmopressin administration to correct hyponatremia. There is a pressing need for better quality research to guide clinicians in managing severe hyponatremia.

 • *The American Journal of Medicine (2015) 128, 1362.e15-1362.e24*

KEYWORDS: DDAVP; Desmopressin; Fluid and electrolyte disorders; Hyponatremia

Funding: The funding organization (HoPingKong Centre for Excellence in Education and Practice) had no role in design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflict of Interest: TEM's work is supported financially by a fellowship from the HoPingKong Centre for Excellence in Education and Practice at the University of Toronto; TT: none; RBC has an administrative role in the HoPingKong Centre for Excellence in Education and Practice at the University of Toronto.

Authorship: TEM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: TEM, TT, RBC.

Acquisition, analysis, or interpretation of data: TEM, TT.

Drafting of the manuscript: TEM.

Critical revision of manuscript for important intellectual content: TEM, TT, RBC.

Obtained funding: TEM.

Study supervision: RBC.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2015.04.040

Hyponatremia is a common clinical problem among inpatients that is associated with adverse outcomes.[1,2] Rapid correction of severe hyponatremia can lead to osmotic demyelination syndrome.[3] Current guidelines, based on expert opinion, recommend correcting serum sodium concentration (sNa) by no more than 8 mEq/L/day for patients at high risk of osmotic demyelination syndrome, and 10-12 mEq/L in 24 hours and 18 mEq/L in 48 hours for patients at average risk of osmotic demyelination syndrome.[4] The use of desmopressin (DDAVP) is recommended to prevent or slow high rates of sNa correction.[4]

There is uncertainty on the optimal timing, dose, and duration of DDAVP in hyponatremia. Some advocate for early DDAVP administration before changes in sNa.[5] Others administer DDAVP at the onset of free water diuresis or when sNa correction has reached[6] or exceeded[7] targets. Co-interventions include normal saline, hypertonic saline, furosemide, and fluid restriction. DDAVP can be given with hypotonic fluids to re-lower sNa, which has been shown to reduce the incidence of osmotic demyelination syndrome in rats.[8,9] DDAVP has potential adverse consequences, such as excessive re-lowering of sNa, neurologic deterioration, or delay in time to resolution of hyponatremia.[10] There is no consensus on a preferred strategy, and the objective of this review is to examine current strategiesfor DDAVP use in hyponatremia.

CLINICAL SIGNIFICANCE

- There are 3 distinct strategies for desmopressin administration in hyponatremia.
- A proactive strategy with early DDAVP may be preferable for high-risk patients.
- Limitations in study design and sample size prevent definitive conclusions.

METHODS

Data Sources

We searched Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (from inception until October 2013) using a combination of keywords for hyponatremia and DDAVP (see **Supplementary Methods**, available online). We updated the search to include studies through October 17, 2014. We hand-searched guidelines, the Cochrane Database of Systematic reviews, and reference lists.

Study Selection

We included randomized controlled trials, observational studies, and systematic reviews in any language. Studies were included if any subjects had sNa $<$ 125 mEq/L and were administered DDAVP. We excluded patients with any of the following: age $<$18 years, recent neurosurgery or traumatic brain injury, vasopressin-receptor antagonist use, hyponatremia complicating DDAVP use for another condition (eg, diabetes insipidus).

Two reviewers (TM and TT) independently screened abstracts to remove irrelevant or duplicate citations. We obtained full-text articles and independently applied inclusion criteria. Studies were excluded if there was insufficient clinical information for analysis. Where clarification was needed, we contacted study authors. For articles not in English or French, we used an online translator (Google Translate, Google Inc, Menlo Park, CA).

Data Extraction and Analysis

The 2 reviewers independently abstracted the data and resolved disagreements by consensus. We recorded the following characteristics: age, sex, diuretic use, psychoactive medication use (including selective serotonin release inhibitors, serotonin-norepinephrine release inhibitors, anticonvulsants, antipsychotic medications), syndrome of inappropriate antidiuretic hormone (SIADH), endocrine disorder (hypothyroidism or adrenal insufficiency), low solute diet (or beer potomania), excess free water intake, liver disease, congestive heart failure, malignancy, alcohol use, seizure on presentation, initial sNa (sNa_i), potassium, and urine osmolality.

We recorded the number, dose, and timing of DDAVP doses. We recorded co-interventions including hypertonic saline, normal saline, potassium, loop diuretics, hypotonic fluids, and fluid restriction.

We recorded the following outcomes: change in sNa at 24 hours (ΔsNa24), change in sNa at 48 hours (ΔsNa48), highest sNa within the first 24 hours, sNa before DDAVP ($sNa_{beforeDDAVP}$), change from sNa_i to $sNa_{beforeDDAVP}$ ($\Delta sNa_{beforeDDAVP}$), time of DDAVP from presentation, lowest sNa within 48 hours after DDAVP, and maximum lowering of sNa after DDAVP, and clinical or magnetic resonance imaging evidence of osmotic demyelination syndrome.

Based on our experience and literature review, we identified 3 strategies for DDAVP administration: 1) proactive, where DDAVP is administered based on the presenting sNa, before changes in clinical parameters; 2) reactive, where DDAVP is administered after a change in clinical parameter (change in sNa or increased urine output); 3) rescue, where DDAVP is administered after exceeding sNa limits or upon development of neurologic symptoms. For the proactive and reactive strategies, DDAVP was used to prevent overcorrection of sNa. In the rescue strategy, DDAVP was used to stabilize or re-lower sNa. We classified cases based on the stated intentions of the study authors where possible. Given that maximum sNa correction thresholds varied between studies, we applied sNa limits as defined by each study when categorizing DDAVP use as "reactive" or "rescue."

For each case, we calculated whether sNa correction exceeded guideline-recommended limits (see **Supplementary Methods**, available online).[4] High risk of osmotic demyelination syndrome included any of: presenting sNa $<$ 106 mEq/L, hypokalemia, alcoholism, malnutrition, or advanced liver disease. For patients at high risk of osmotic demyelination syndrome, we defined the sNa correction limit