



Fatal Hyponatremia Associated with Preoperative Desmopressin for Bleeding Disorder

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Abstract

We report a 21-year-old male who underwent surgical repair of facial fractures 5 days following trauma. The patient developed rapidly progressive hyponatremia (serum sodium nadir, 123 mmol/l) and acute cerebral edema that progressed to transtentorial herniation and death following prophylactic desmopressin (20 µg) given 30 minutes preoperatively for congenital platelet function defect. Other contributing factors included a preceding 3-day prodrome of hypernatremia secondary to neurogenic diabetes insipidus (which may have made the brain more susceptible to injurious effects of perioperative acute hyponatremia) and intra-/postoperative administration of large volumes of crystalloid. This fatal adverse effect of desmopressin underscores the need for careful patient selection when using this prohemostatic agent with a major antidiuretic (water-retaining) profile.

Key words: Desmopressin, Brain injury, Trauma

Background

Desmopressin acetate, also known as 1-deamino-8-D-arginine vasopressin (DDAVP), is a vasopressin analogue that is commonly given to prevent or treat hypernatremia in the setting of central diabetes insipidus [1]. Compared with native antidiuretic hormone (ADH), desmopressin exhibits tenfold greater antidiuretic power, with only 0.05% of the vasopressor activity [2]. Another effect is stimulation of the endothelium to release von Willebrand factor, making desmopressin a common agent used to prevent or treat bleeding in patients with hemostatic abnormalities such as mild or moderate von Willebrand disease [3] or various platelet function disorders [4,5] or as a general prohemostatic agent to reduce transfusion needs after surgery [6]. A potential adverse effect is hyponatremia, which can be sufficiently severe to result in seizures [7,8] or coma [9]. We report a patient who developed rapid-onset of hyponatremia, manifest as cerebral edema that progressed to transtentorial herniation and brain death, associated with the use of preoperative desmopressin given to reduce risk of bleeding in a young man with congenital platelet abnormality. This represents an example of a fatal complication related to the use of a common blood conservation technique.

Case

A 21-year-old male was involved in a motor vehicle accident

resulting in decreased level of consciousness (Glasgow coma scale, 6) requiring intubation, hypotension responding to fluid administration, and a hemoglobin fall to 80 g/l. He sustained Lefort I and II fractures and a basal skull fracture with an associated small right subdural hematoma, right frontal and left posterior parietal contusions, but no associated mass effect or midline shift. Neurogenic (post-head injury) diabetes insipidus was diagnosed on the basis of hypernatremia (serum sodium, 151 mmol/l; serum osmolality, 306 mmol/kg [normal range, 280-300 mmol/kg]) and inappropriate urine hypoosmolality (urine osmolality, 109 mmol/kg), and was treated with 2 µg infusions of desmopressin given four times during the first four hospital days (Figure 1A-C).

He also received cryoprecipitate and platelet transfusion on admission, followed by daily platelet transfusions, both because of his intracerebral hemorrhages, and because of a documented bleeding disorder that was first investigated after he developed severe post-tonsillectomy bleeding at age 3. Previous investigations had revealed a non-specified platelet function defect characterized by abnormal platelet aggregation to multiple agonists (including absent aggregation to the thromboxane analogue, U46619; delayed response to collagen and borderline response to arachidonic acid). On a previous occasion, his prolonged bleeding time (20 minutes; normal 2.5-8.5 min) shortened to 11.5 minutes following intravenous

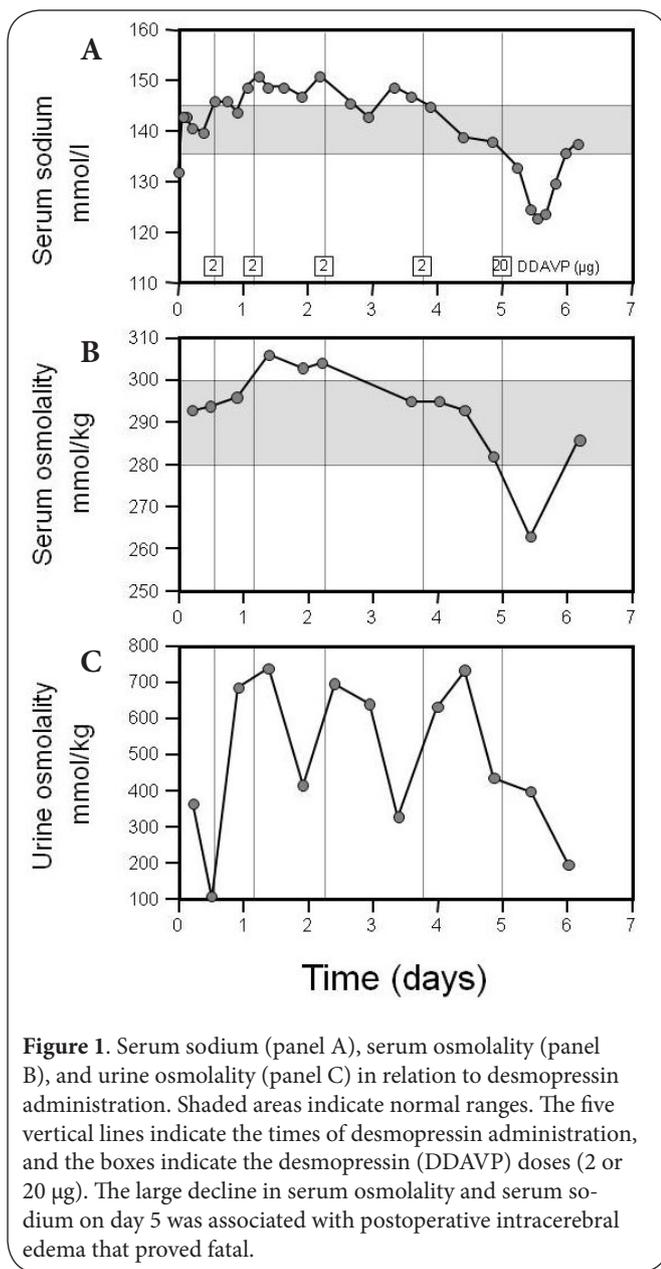


Figure 1. Serum sodium (panel A), serum osmolality (panel B), and urine osmolality (panel C) in relation to desmopressin administration. Shaded areas indicate normal ranges. The five vertical lines indicate the times of desmopressin administration, and the boxes indicate the desmopressin (DDAVP) doses (2 or 20 µg). The large decline in serum osmolality and serum sodium on day 5 was associated with postoperative intracerebral edema that proved fatal.

desmopressin. The patient also had been shown to have low-normal levels of von Willebrand factor (antigen, 0.75 [normal, 0.50-1.50 U/ml]; ristocetin cofactor activity, 0.65 [normal, 0.50-1.50 U/ml]).

Repeated neurologic assessment in the first five hospital days revealed response to verbal prompts, localization to pain, movement of all four limbs, pupils equal (3 mm) and reactive. On day five, he underwent surgical repair of Lefort I and II facial fractures. He remained intubated and ventilated, receiving midazolam 15 mg/h and morphine 25 mg/h for

sedation and analgesia. Laboratory values on the morning of surgery included a hemoglobin of 81 g/L, platelet count $172 \times 10^9/l$, international normalized ratio (INR) 1.1, activated partial thromboplastin time (APTT) 27 sec, urea 2.0 mmol/l, creatinine 37 µmol/l, sodium 138 mmol/l, potassium 3.4 mmol/l, chloride 106 mmol/l, serum osmolality 282 mmol/kg. To secure hemostasis, the following treatment plan was implemented: desmopressin, 20 µg (maximum dose for patient weighing 94 kg) 30 minutes prior to surgery (ordered by the hematology service); tranexamic acid (anti-fibrinolytic agent), 1 g iv q8h; and platelets as required.

General anesthesia was induced with propofol and rocuronium, and maintained with oxygen/air mixture and 2.0-2.5% end-tidal sevoflurane. Surgery was performed without technical difficulties or need for platelet or cryoprecipitate transfusions; there was moderate blood loss (~1000 ml). During the 5.5 h surgery, the patient received 6250 ml crystalloid (5000 ml Ringer's lactate; 1250 ml 0.9% sodium chloride), 1000 ml pentaspan, and 2 units of red cell concentrates. Intraoperative urine output was approximately 1000 ml.

Postoperatively, the intravenous fluid was changed to 2/3 D5W-1/3 isotonic saline, given at 150 ml/h. Blood work on arrival to the intensive care unit showed hemoglobin 66 g/l, platelet count $146 \times 10^9/l$, INR 1.2, APTT 31 s, urea 2.1 mmol/l; creatinine 33 µmol/l; sodium 133 mmol/l, potassium 3.9 mmol/l, chloride 102 mmol/l, and glucose 6.3 mmol/l. Four hours later the patient developed seizures. His pupils were fixed and dilated, he was non-responsive to stimuli, and no brainstem reflexes could be elicited. At this time, the patient's serum sodium had fallen to 123 mmol/l, and the serum osmolality was only 263 mmol/kg. A CT scan showed cerebral edema, with 5 mm midline shift and subfalcine transtentorial and cerebellar tonsillar herniation; previous areas of contusion seen on admission CT imaging were unchanged. The neurologic status did not improve after decompressive craniectomy and insertion of a ventricular drain; brain death was declared after repeat CT scan imaging showed severe diffuse cerebral edema and loss of gray-white differentiation. Post-mortem examination showed acute severe cerebral edema as well as parenchymal hemorrhage consistent with the history of head trauma 5 days earlier.

Discussion

Several lines of evidence suggest that desmopressin-associated hyponatremia—occurring in the setting of liberal intra-/postoperative administration of crystalloid—played a significant contributory role in the cerebral edema and transtentorial herniation. The serum osmolality fell from 293 to 263 mmol/kg over 24 hours, with the largest component of this fall (from 282 to 263 mmol/kg) occurring in association with desmopressin administration. The corresponding abrupt desmopressin-associated decline in serum sodium was from 138 to 123 mmol/l. Relatively low urine volumes were observed during and within 4 hours of surgery

(2000 ml urine volume compared with 8400 ml intravenous fluids administered); further, the postoperative urine osmolality (400 mmol/kg) was inappropriately concentrated in relation to the serum sodium concentration of 123 mmol/l, implicating the antidiuretic effects of desmopressin.

In addition, cerebral edema is a known consequence of severe, acute hyponatremia [10,11]. Brain cells are able to adapt to hyponatremia if it occurs slowly, by exporting intracellular potassium and chloride and organic osmolytes including taurine, glutamine, glycerophosphorylcholine and myoinositol [12]. This allows maintenance of brain cell volume. A review [13] of published cases of hyponatremia suggested that humans tolerate hyponatremia if the rate of decrease of serum sodium concentration is ≤ 0.5 mmol/l/h. In this case, the decrease in serum sodium from 138 to 123 mmol/l over approximately 16 hours, a rate of change of 0.92 mmol/l/h, was considerably higher than the rate that the brain can adapt to, and almost certainly was the most important factor leading to acute cerebral edema.

In this patient, the consequences of acute hyponatremia may have been exacerbated by the hypernatremic prodrome (related to neurogenic diabetes insipidus) (Figure 1A). Given that brain cells adapt to hypernatremia by increasing brain solute content, we conjecture that the preceding three-day period of hypernatremia may have made the brain less able to respond to the subsequent acute hyponatremia, since it was recently in the process of responding to an increase in serum sodium concentration.

Other potential contributing effects were the patient's brain injuries secondary to trauma sustained five days earlier and the concurrent surgery for this; thus, the role of delayed onset of cerebral edema from preceding head trauma alone cannot be ruled out. However, the close temporal relationship between onset of seizures, coma, and brain death, and desmopressin-associated hyponatremia, implicate at least an important contributory—if not predominant—role of desmopressin in explaining the patient's abrupt neurological demise.

Symptomatic hyponatremia is a common complication of prophylactic use of desmopressin for bleeding disorders, especially in young patients. A prospective study of 41 children with von Willebrand disease who received desmopressin for otolaryngologic surgery found mild hyponatremia (130-135 mmol/l) in 66% of patients, and severe hyponatremia (<130 mmol/l) in two (5%) patients, one of whom developed seizures [14]. A retrospective study of 53 children who underwent serum sodium measurements after receiving prophylactic intravenous desmopressin for von Willebrand's disease and adenotonsillectomy found that 51% developed mild hyponatremia, and 3 (6%) developing severe hyponatremia, one with seizures [15]. A series of 19 adults receiving intranasal desmopressin for von Willebrand disease or hemophilia found that 32% developed symptoms consistent with hyponatremia, with 1 patient developing severe hyponatremia

(serum sodium, 124 mmol/l) [16]. Recognized risk factors for desmopressin-associated hyponatremia include the young and the elderly, multiple doses, perioperative stress (elevated endogenous ADH levels), and administration of hypotonic fluids. Our patient was relatively young, had undergone major surgery, and was given hypotonic fluids postoperatively, illustrating the potential risk when transfer of care occurs and the implications of earlier administration of desmopressin are not recognized.

There are few examples in the literature of patients who have developed fatal complications associated with use of blood avoidance techniques. For example, a patient has been reported who developed fatal anaphylaxis associated with use of aprotinin given as a blood-conserving technique [17]. In our patient, fatal hyponatremia occurred in association with use of a common blood conserving medication, desmopressin, when relatively large volumes of intra-/postoperative crystalloid were given in the setting of recent hypernatremia. Given the known antidiuretic effects of desmopressin, with the potential for inducing hyponatremia and cerebral edema, the severe clinical course illustrates the importance of careful patient selection and appropriate perioperative management (e.g., avoiding excessive fluid administration) to ensure that the risk-benefit relationship of this blood conservation technique is optimal.

Competing interests

The authors declare that they have no competing financial or other interests.

Authors' contributions

JSM and TEW abstracted the clinical information; all four authors interpreted the data and wrote the manuscript.

Acknowledgements and funding

The corresponding author (T.E.W.) is funded by the Heart and Stroke Foundation of Ontario. The authors thank Jo-Ann I. Sheppard for preparing the figure.

Publication history

Editor: Paul Picton, University of Michigan, USA.

Received: 28-May-2012 Revised : 10-Aug-2012

Accepted: 24-Aug-2012 Published: 15-Sep-2012

References

1. Cobb, W. E., Spare, S. & Reichlin, S.: **Neurogenic diabetes insipidus: management with dDAVP (1-desamino-8-D arginine vasopressin)**. *Ann Intern Med* 1978, **88**(2):183-188. | [Article](#) | [PubMed](#)
2. Goldsmith SR.: **Vasopressin as a vasopressor**. *Am J Med* 1987, **82**(6):1213-1219. | [Article](#)
3. Mannucci, P. M.: **Treatment of von Willebrand's Disease**. *N Engl J Med* 2004, **351**(7):683-694. | [Article](#) | [PubMed](#)
4. DiMichele, D. M. & Hathaway, W. E.: **Use of DDAVP in inherited and acquired platelet dysfunction**. *Am J Hematol* 1990, **33**(1):39-45. | [Article](#) | [PubMed](#)
5. Rao, A. K. et al.: **Mechanisms of platelet dysfunction and response to DDAVP in patients with congenital platelet function defects. A double-blind placebo-controlled trial**. *Thromb Haemost* 1995, **74**(4):1071-1078. | [Article](#) | [PubMed](#)
6. Crescenzi, G. et al.: **Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials**. *Anesthesiology* 2008,

- 109(6):1063-1076. | [Article](#) | [PubMed](#)
7. Weinstein, R. E. *et al.*: **Severe hyponatremia after repeated intravenous administration of desmopressin.** *Am J Hematol* 1989, **32**(4):258-261. | [Article](#) | [PubMed](#)
 8. Bertholini, D. M. & Butler, C. S.: **Severe hyponatraemia secondary to desmopressin therapy in von Willebrand's disease.** *Anaesth Intensive Care* 2000, **28**(2):199-201. | [Article](#) | [PubMed](#)
 9. Gomez Garcia, E. B., Ruitenber, A., Madretsma, G. S. & Hintzen, R. Q.: **Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease.** *Haemophilia* 2003, **9**(2):232-234. | [Article](#) | [PubMed](#)
 10. Arieff, A. I., Llach, F. & Massry, S. G.: **Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes.** *Medicine (Baltimore)* 1976, **55**(2):121-129. | [Article](#) | [PubMed](#)
 11. Gross, P., Reimann, D., Henschkowski, J. & Damian, M.: **Treatment of severe hyponatremia: conventional and novel aspects.** *J Am Soc Nephrol* 2001, **12** Suppl (17):S10-S14. | [Article](#) | [PubMed](#)
 12. Pasantes-Morales, H., Lezama, R. A., Ramos-Mandujano, G. & Tuz, K. L.: **Mechanisms of cell volume regulation in hypo-osmolality.** *Am J Med* 2006, **119**(7 Suppl 1):S4-11. | [Article](#) | [PubMed](#)
 13. Cluitmans, F. H. & Meinders, A. E.: **Management of severe hyponatremia: rapid or slow correction?** *Am J Med* 1990, **88**(2):161-166. | [Article](#) | [PubMed](#)
 14. Jimenez-Yuste, V. *et al.*: **Otolaryngologic surgery in children with von Willebrand disease.** *Arch Otolaryngol Head Neck Surg* 2002, **128**(12):1365-1368. | [Article](#) | [PubMed](#)
 15. Allen, G. C. *et al.*: **Adenotonsillectomy in children with von Willebrand disease.** *Arch Otolaryngol Head Neck Surg* 1999, **125**(5):547-551. | [Article](#) | [PubMed](#)
 16. Dunn, A. L. *et al.*: **Adverse events during use of intranasal desmopressin acetate for haemophilia A and von Willebrand disease: a case report and review of 40 patients.** *Haemophilia* 2000, **6**(1):11-14. | [Article](#) | [PubMed](#) Abstract | [PubMed](#) Full Text
 17. Oswald, A. M. *et al.*: **Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue.** *Anesthesiology* 2003, **99**(3):762-763. | [Article](#) | [PubMed](#)

Citation:

Milkovic J S, Warkentin T E, Richardson R M A and Prebtani A P H: **Fatal Hyponatremia Associated with Preoperative Desmopressin for Bleeding Disorder.** *Journal of Anesthesiology and Clinical Science* 2012, **1**:11.
http://dx.doi.org/10.7243/2049-9752-1-11