Therapeutic Relowering of Plasma Sodium after Overly Rapid Correction of Hyponatremia
What Is the Evidence?

Helbert Rondon-Berrios

CJASN 15: 282–284, 2020. doi: https://doi.org/10.2215/CJN.04880419

Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Correspondence: Dr. Helbert Rondon-Berrios, Renal-Electrolyte Division, University of Pittsburgh School of Medicine, 3550 Terrace Street, A915 Scaife Hall, Pittsburgh, PA 15261. Email: rondonberriosh@upmc.edu

Introduction

Overly rapid correction of hyponatremia is defined as a plasma sodium correction rate exceeding the recommended limits, but controversy still exists about what those limits are. Two common limits used are (*1*) >10–12 mEq/L in the first 24 hours and >18 mEq/L in the first 48 hours; and (*2*) >8 mEq/L in any 24-hour period. Excessive correction of hyponatremia frequently occurs when treatment of the underlying cause restores the kidneys' ability to excrete diluted urine. Overly rapid correction of chronic (>48 hours) hyponatremia results in brain dehydration, rendering it susceptible to the osmotic demyelination syndrome. Osmotic demyelination syndrome is extremely rare in patients with plasma sodium >120 mEq/L (incidence as low as 0.6 per million person-years). However, in patients with plasma sodium ≤105 mEq/L, the incidence may be as high as 50% and alcohol use disorder is a recognized risk factor. Several animal models have facilitated the understanding of its pathogenesis: in one prevalent model, rats are induced with severe (plasma sodium <115 mEq/L) hyponatremia by administration of vasopressin (or an analog) and hypotonic fluids, which are then maintained for 3 days, after which plasma sodium is overcorrected, allowing a correction gradient of 20–25 mEq/L per day required for the occurrence of demyelination (1). This model has limitations as a single intraperitoneal injection of hypertonic saline is given, causing a large plasma sodium change in a few hours. Initial observations suggested that blood-brain barrier disruption and microglial activation were the primary events in osmotic demyelination syndrome, but more recent studies suggest that early astrocyte and oligodendrocyte necroptosis causing disruption of the astrocyte-oligodendroglial syncytium may be the initial event occurring before demyelination. Another development is the recognition that the magnitude of daily plasma sodium rise, rather than the hourly correction rate, is critical for the development of demyelination (2), which led investigators to hypothesize that the process resulting in demyelination remains reversible for some time after overly rapid correction, and intervening by plasma sodium relowering during this period could prevent this complication.

In this manuscript, we review the evidence for plasma sodium relowering after excessive correction of hyponatremia and offer some recommendations.

Plasma Sodium Relowering after Excessive Correction of Hyponatremia in Individuals without Clinical Manifestations of Osmotic Demyelination Syndrome

Soupart *et al.* (3) investigated the reversibility of the process leading to osmotic demyelination syndrome using the animal model of excessive correction previously described. The investigators compared three interventions: plasma sodium relowering to a correction gradient <20 mEq/L per day, relowering to a correction gradient >20 mEq/L per day, and no relowering. Mortality, demyelination symptoms, and histologic severity of demyelination were significantly lower in the group that underwent relowering to a correction gradient <20 mEq/L per day.

In another study, Gankam Kengne *et al.* (4), using a similar model, treated animals with dexamethasone, plasma sodium relowering to a correction gradient <20 mEq/L per day, or no therapy. Both dexamethasone and plasma sodium relowering prevented blood-brain barrier opening and decreased microglial activation and demyelination symptoms. However, only relowering reduced mortality.

The feasibility and safety of plasma sodium relowering have been examined in three retrospective studies. Perianayagam *et al.* (5) performed a retrospective study at a community teaching hospital over 6 years and identified 20 patients who received desmopressin as part of hyponatremia therapy. Desmopressin and 5% dextrose in water (D5W) were given after a plasma sodium change ≥12 mEq/L in 24 hours in six patients, which resulted in a plasma sodium 4–9 mEq/L lower than the peak and prevented it from exceeding >18 mEq/L by 48 hours in five patients. Cerebral edema is a concern during plasma sodium relowering. During adaptation to hyponatremia, the brain minimizes swelling by extruding solutes, a process fully achieved by 48 hours. However, re-establishment of intracellular solutes during

rapid correction of hyponatremia occurs at a slower pace (5–7 days), which minimizes the risk of brain edema during plasma sodium relowering. All of the patients in this study tolerated relowering with absence of neurologic symptoms.

Rafat *et al.* (6) performed a retrospective study of 20 patients with plasma sodium <120 mEq/L admitted to two intensive care units who were treated with desmopressin. Plasma sodium relowering occurred in 11 patients. This was accomplished by the coadministration of hypotonic fluids. All of these 11 patients corrected their plasma sodium by <18 mEq/L in 48 hours. The mean plasma sodium reduction was 5.1±2.6 mEq/L and no seizures were observed during relowering.

MacMillan and Cavalcanti (7) performed a retrospective study of 1450 admissions with hyponatremia (plasma sodium <123 mEq/L) at two academic hospitals over 10 years. Desmopressin was administered in 254 admissions (17.5%). The investigators identified three desmopressin strategies: (*1*) proactive, *i.e.*, desmopressin was administered with hypertonic saline from the outset of therapy to achieve a slow correction, in 11% of admissions; (*2*) reactive, *i.e.*, desmopressin was administered upon the onset of rapid correction or increased urine output to maintain plasma sodium under correction limits, in 68.5%; and (*3*) rescue, *i.e.*, desmopressin was administered with hypotonic fluids after overly rapid correction already occurred to relower plasma sodium just under correction limits, in 18.1%. Compared with patients who did not receive desmopressin, fewer patients receiving desmopressin achieved a plasma sodium correction <12 mEq/L in 24 hours (84.5% versus 70.9%; $P<0.01$) and <18 mEq in 48 hours (92.3% versus 86.5%; $P=0.005$) and these results were driven by a rescue strategy, likely representing cofounding by indication because desmopressin was more likely to be given after rapid correction had occurred. Nevertheless, 60.9% of patients treated with the rescue strategy corrected plasma sodium to <18 mEq/L by 48 hours. Hypotonic fluids were administered in 90 patients (35.9%), and most commonly as a part of the rescue strategy. The median reduction in plasma sodium was 9 mEq/L. Likewise, no adverse consequences from relowering were observed.

MacMillan *et al.* (8) conducted a systematic review of all published literature on desmopressin use for excessive correction of hyponatremia (plasma sodium <125 mEq/L). The investigators included 17 studies of low-to-moderate quality with a total of 80 patients. A rescue strategy was reported in nine studies. Plasma sodium change at 24 and 48 hours with a rescue strategy were 15.6±3.1 mEq/L and 16.6±4.7 mEq/L, respectively. The maximum plasma sodium lowering achieved was 8.2±4 mEq/L in 24 hours. No reports of harm from relowering occurred.

Plasma Sodium Relowering after Excessive Correction of Hyponatremia in Individuals with Early Clinical Manifestations of Osmotic Demyelination Syndrome

Soupart *et al.* (9) explored the hypothesis that the osmotic demyelination syndrome remains reversible even after the onset of its early neurologic manifestations. Using the animal model of rapid correction, animals that experienced neurologic manifestations compatible with demyelination were selected and divided them in two groups: one was subjected to plasma sodium relowering 4–10 hours after excessive correction reaching a correction gradient <20 mEq/L per day, and the other group was left overcorrected. The neurologic manifestations of demyelination were attenuated or disappeared after plasma sodium relowering. Six-day survival after excessive correction in this latter group was 46.6% compared with 7% in the group left overcorrected ($P<0.03$). The timing of the intervention was important: animals that underwent relowering at 4 hours had better survival than those that waited up to 8–10 hours to undergo relowering (8.7±1.4 days versus 5.6±3.1 days, respectively; $P<0.05$).

Furthermore, the systematic review by MacMillan *et al.* (8) showed that the rescue strategy reversed the manifestations of imminent osmotic demyelination syndrome in four patients. In addition, several case reports have documented the efficacy and safety of plasma sodium relowering in patients with early manifestations of osmotic demyelination syndrome (10). It is worth noting that case studies showing symptom improvement after relowering are difficult to interpret, because some patients with osmotic demyelination syndrome may improve spontaneously.

Recommendations

The author's approach to therapeutic relowering of plasma sodium in the setting of overly rapid correction of hyponatremia is outlined below.

- Therapeutic relowering of plasma sodium should be considered in patients with severe hyponatremia (plasma sodium <120 mEq/L) of chronic (>48 hours) or unknown duration who experience overly rapid correction particularly if risk factors for osmotic demyelination syndrome are present (*i.e.*, alcohol use disorder, cirrhosis, malnutrition, hypokalemia, and plasma sodium ≤105 mEq/L) with a goal of bringing the plasma sodium just under the correction limit (strength of recommendation: expert opinion; quality of evidence: low).
- Plasma sodium relowering should also be considered in patients with early manifestations of osmotic demyelination syndrome (*e.g.*, altered mental status, seizures, paresis, dysarthria, ataxia, and oculomotor abnormalities) (strength of recommendation: expert opinion; quality of evidence: low).
- Plasma sodium relowering is best accomplished by the coadministration of desmopressin and D5W. Desmopressin is given at a dose of 2–4 mcg intravenously or subcutaneously every 6–8 hours. This halts further water diuresis although the effect might be reduced in patients treated with vasopressin antagonists. D5W is administered as an intravenous infusion at a rate of 3 ml/kg per hour. This rate will decrease plasma sodium by approximately 1 mEq/L per hour (strength of recommendation: expert opinion; quality of evidence: low).
- Once target plasma sodium is achieved, consider stopping D5W but continuing desmopressin to prevent further correction. Hypertonic saline (NaCl 3%) may be added after 24–48 hours to continue slow correction. Desmopressin and hypertonic saline can then be discontinued when plasma sodium reaches 125 mEq/L (strength of recommendation: expert opinion; quality of evidence: low).

Conclusions

Data from animal studies, case reports, and case series suggests that the process leading to osmotic demyelination syndrome remains reversible for a period of time after overly rapid correction of hyponatremia, even when neurologic manifestations of early osmotic demyelination syndrome occur. This represent an opportunity to intervene by relowering plasma sodium with the coadministration of desmopressin and D5W to prevent or treat impeding osmotic demyelination syndrome.

Acknowledgments

The author would like to thank Dr. Richard H. Sterns for his helpful comments on a prior version of this manuscript. The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or *CJASN*. Responsibility for the information and views expressed therein lies entirely with the author(s).

Disclosures

Dr. Rondon-Berrios has nothing to disclose.

References

1. Soupart A, Stenuit A, Perier O, Decaux G: Limits of brain tolerance to daily increments in serum sodium in chronically hyponatraemic rats treated with hypertonic saline or urea: Advantages of urea. *Clin Sci (Lond)* 80: 77–84, 1991
2. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G: Treatment of chronic hyponatremia in rats by intravenous saline: Comparison of rate versus magnitude of correction. *Kidney Int* 41: 1662–1667, 1992
3. Soupart A, Penninckx R, Crenier L, Stenuit A, Perier O, Decaux G: Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering. *Kidney Int* 45: 193–200, 1994
4. Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G: Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int* 76: 614–621, 2009
5. Perianayagam A, Sterns RH, Silver SM, Grieff M, Mayo R, Hix J, Kouides R: DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 3: 331–336, 2008
6. Rafat C, Schortgen F, Gaudry S, Bertrand F, Miguel-Montanes R, Labbé V, Ricard JD, Hajage D, Dreyfuss D: Use of desmopressin acetate in severe hyponatremia in the intensive care unit. *Clin J Am Soc Nephrol* 9: 229–237, 2014
7. MacMillan TE, Cavalcanti RB: Outcomes in severe hyponatremia treated with and without desmopressin. *Am J Med* 131: 317.e1–317.e10, 2018
8. MacMillan TE, Tang T, Cavalcanti RB: Desmopressin to prevent rapid sodium correction in severe hyponatremia: A systematic review. *Am J Med* 128: 1362.e15–1362.e24, 2015
9. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G: Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms. *J Neuropathol Exp Neurol* 55: 594–601, 1996
10. Soupart A, Ngassa M, Decaux G: Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. *Clin Nephrol* 51: 383–386, 1999

Published online ahead of print. Publication date available at www.cjasn.org.