Risk Factors, Complication and Measures to Prevent or Reverse Catastrophic Sodium Overcorrection in Chronic Hyponatremia

Kamel A. Gharaibeh, MD, Joseph M. Brewer, DO, Mohit Agarwal, MD and Tibor Fülöp, MD

Abstract: Hyponatremia is the most common electrolyte disorder encountered in clinical practice. Patients who develop this condition for more than 48 hours are at risk for severe neurological sequelae if correction of the serum sodium occurs too rapidly. Certain medical disorders are known to place patients at an increased risk for rapid correction of serum sodium concentration. Large-volume polyuria in this setting is an ominous sign. For these patients, early identification of risk factors, close monitoring of serum sodium correction and the use of 5% dextrose with or without desmopressin to prevent or reverse overcorrection are important components of treatment.

Key Indexing Terms: Desmopressin; Hyponatremia; Osmotic demyelination syndrome; Polyuria; Syndrome of inappropriate antidiuretic hormone secretion. **[Am J Med Sci 2015;349(2):170–175.]**

Hyponatremia is typically defined as a serum sodium concentration <135 mEq/L and is the most common electrolyte disorder encountered in clinical practice.[1–3] The condition can develop in <24 hours and can cause profound neurological disturbances that require emergent treatment.[4] Chronic hyponatremia lasting more than 48 hours can be caused by a host of distinct entities, including diuretic use, inappropriate antidiuresis or a number of chronic medical conditions.[4]

CHRONIC HYPONATREMIA

Most cases of chronic hyponatremia are relatively asymptomatic[5] because of the chronic nature of hyponatremia developing over a period of time sufficient for cerebral adaptation. Notwithstanding, recent research has reported increased odds of falls[6,7] and higher all-cause mortality[6] in elderly persons with mild hyponatremia. Other studies of large cohorts have demonstrated significantly higher in-hospital mortality in persons with hyponatremia at[3,8] or during[8] admission. Chronic hyponatremia has also been reported to cause impaired cognition, gait disturbance and (rarely) seizures.[9] Perhaps, the greatest danger for patients with chronic hyponatremia concerns the correction and recovery phase, as a rapid or extreme increase in serum sodium may lead to neurological injury in brain cells that may have become adapted to low serum osmolality over time.[2,9–11]

Current understanding of hyponatremia treatment is generally guided by the principles of increasing exchangeable electrolytes (namely sodium), decreasing total body water or both.[10] The method, and most importantly the rate,[9] of correction is usually determined by the onset and duration of hyponatremia. At this time, there is no single ideal treatment owing to the association of hyponatremia with multiple etiologies and different pathophysiological mechanisms.[10] There are no randomized controlled trials to guide treatment of hyponatremia.[5,9] Instead, evidence for current treatment practice rests in observational studies and experimental animal models.[5,9] Patients with symptoms as a result of hyponatremia are treated with a brief infusion of 3% saline with the goal of increasing the serum sodium concentration 2 to 4 mEq/L over 2 to 4 hours followed by slow correction maintained at <10 mEq/L in 24 hours or <18 mEq/L in 48 hours.[10] Multiple equations are available to help calculate the initial rate of fluids to be administered. A widely used formula is the Adrogue-Madias formula[12]: Change in serum Na^+ with infusing solution = (infusate Na^+ + infusate K^+) − serum Na^+/(total body water +1). Accuracy of this formula, however, is disputed and investigators have reported conflicting results.[13,14] The initial infusion rate (mL/hr) of 3% saline can also be simply calculated as a product of patients' weight (kg) and desired correction rate ($mEq \cdot L^{-1} \cdot hr^{-1}$) as demonstrated by Verbalis et al.[5] In an emergent situation, a rapid infusion of 100 mL of 3% saline can be used to acutely raise the sodium concentration by 2 to 4 mEq/L. This infusion can be repeated in about half an hour if no clinical improvement is seen. Frequent monitoring of serum sodium concentration must be performed to adjust this initial infusion rate to prevent inadvertent rapid correction. Patients with asymptomatic chronic nonhypovolemic hyponatremia may be treated with fluid restriction to less than the rate of urinary water excretion[5] though adherence to this treatment is often difficult,[4] and the rate of correction is often a paltry 1 to 2 $mEq \cdot L^{-1} \cdot d^{-1}$. Fluid restriction is unlikely to work if the effective urine osmolality (twice the sum of urine sodium and potassium) is greater than twice the serum sodium concentration.

An accurate assessment of the volume status in hyponatremic subjects is crucial to optimize the treatment strategy in affected individuals. Isotonic saline is the recommended therapy for hypovolemic hyponatremia; however, saline infusion could worsen hyponatremia especially if a patient has elevated levels of arginine vasopressin (AVP) as may be the case in a patient who develops hypovolemic hyponatremia secondary to gastroenteritis associated with nausea.[4] Normal saline should be avoided in hypervolemic hyponatremia due to potential worsening of volume overload. A loop diuretic such as furosemide is sometimes prescribed with saline or salt tablets in patients with a syndrome of inappropriate antidiuresis to facilitate excretion of hypotonic urine.[15] In Belgium, urea has been used to correct severe hyponatremia, but the effect is not predictable because the increase in serum sodium level depends on urea excretion and kidney function, which would be expected to vary with volume status and AVP level. Decaux et al[16] reported the use of intravenous or oral urea to treat patients with a serum sodium level <115 mEq/L, but more than one-third of the patients with a serum sodium level <120 mEq/L had excessive correction. Use of mineralocorticoids for the management of hyponatremia is limited in the United

From the Department of Internal Medicine, University of Mississippi Medical Center, Jackson, Mississippi.

Submitted February 15, 2013; accepted in revised form July 11, 2014. The authors have no financial or other conflicts of interest to disclose.

Correspondence: Kamel A. Gharaibeh, MD, Department of Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505 (E-mail: kamelgharaibeh@yahoo.com).

States, in part because of concerns about mineralocorticoid-associated fluid overload. A tetracycline antibiotic, demeclocycline, exhibits vasopressin-2 receptor antagonist (V2RA) properties and has been used successfully in syndrome of inappropriate antidiuresis.[17] It is, though, not FDA approved for this indication and can cause reversible nephrotoxicity, especially in people with cirrhosis and heart failure.[18,19] Intravenous conivaptan and oral tolvaptan are 2 V2RA currently available in the United States. They are FDA approved for the management of hypervolemic and euvolemic hyponatremia, though some restrictions apply, including treatment durations limited to 4 days for conivaptan to minimize the possibility of CYP3A4 drug interactions and 30 days for tolvaptan to minimize the risk of liver injury. In a meta-analysis that included 15 randomized controlled trials, vasopressin receptor antagonists were shown to have early and late efficacy in normalizing or significantly increasing serum sodium concentration. The same meta-analysis also identified an increased rate of rapid sodium correction without neurological injury[20] with the use of V2RA, though the latter might have been averted during the controlled trials because of the exclusion of high-risk patients and the careful monitoring of the study subjects. In patients with chronic and otherwise asymptomatic hyponatremia, the approximate limits of osmolality change are less than 10 to 12 mEq/L in 24 hours[4,5,9,10,21] and less than 18 mEq/L in 48 hours with a tendency toward less correction over time in patients at risk for neurological injury.[5,9,10,21] To further decrease risk and to afford margins of safety, Adrogue and Madias[22] suggested to correct hyponatremia by maximum increment of 8 mEq/L in the sodium level in 24-hour period.

BRAIN RESPONSE TO HYPONATREMIA

The brain has mechanisms that allow it to adapt to a changing osmotic environment. Sodium is an effective solute and does not cross cell membranes easily; thus, acutely, only water can flow in and out of brain cells in response to changes of extracellular tonicity.[9,10] Brain cells also contain high concentrations of organic osmolytes that can be translocated to the extracellular space in the setting of hyponatremia.[10] When hyponatremia develops in $<$24 hours, this may lead to brain edema due to the inability of compensatory mechanisms to adapt quickly (osmolytes shift). When, however, hyponatremia develops chronically, brain cells are able to export osmolytes and import water to equilibrate intracellular osmolality with extracellular osmolality without cellular swelling.[5,7,9,10] Once adapted to a state of chronic hyponatremia, rapid correction of serum sodium concentration may overwhelm the ability of brain cells to regain lost osmolytes,[2,4,5,10] which may take up to 1 week to occur.[10]

OSMOTIC DEMYELINATION SYNDROME

Osmotic demyelination syndrome (ODS) is a rare[1,9] but well-established complication of rapid correction of chronic hyponatremia that was reported by Sterns et al[11] in a seminal article describing 8 patients who developed cerebral demyelination. Adaptation that allows the brain to survive chronic hyponatremia makes the brain more susceptible to cellular damage when serum sodium concentration is increased quickly because of the impairment of normal defenses that prevent osmotic shrinking as a result of prolonged hyponatremia.[4] ODS is marked by programmed death of oligodendrocytes in myelin-rich areas of the brain.[23]

Patients with ODS have variable presentations ranging from relatively few symptoms[9] to new progressive neurological deficits[5] that develop 1 to several days after correction of chronic hyponatremia.[4,10] Symptom development begins with lethargy and behavioral changes, followed by mutism or dysarthria, spastic quadriparesis and pseudobulbar palsy.[2,4,20] Numerous risk factors for the development of ODS have been identified (Table 1).[2,5,9,10,21,23] Patients with these risk factors should have serum sodium correction carefully monitored with a maximum correction of 8 $mEq \cdot L^{-1} \cdot d^{-1}$. Outcomes in patients with ODS vary. Some reports describe patients having transient, reversible neurological dysfunction,[1,4,10] whereas other authors describe frequent aspiration with the need for mechanical ventilation in patients with ODS.[10] Overall, most patients survive,[5,10] although death has been reported.[11]

Upon presentation of severe chronic symptomatic hyponatremia, the concern about ODS does not justify therapeutic inaction, but the fear of complications from hyponatremic encephalopathy does not justify therapeutic excess. Some patients with symptomatic chronic hyponatremia develop cerebral edema, which makes it a medical emergency. Fortunately, we need minimal correction in serum sodium concentration by 4 to 6 mEq/L to take these patients out of the risk zone and reverse the cerebral edema or relieve the symptoms[24] while we are trying not to overcorrect and put the patients at risk of ODS. In fact in a study by Koenig et al,[25] rapid rise in serum sodium by 5 mEq/L was shown to significantly reduce intracranial pressure. Unfortunately, it is challenging to keep most hyponatremic patients in the safe zone of correction, especially if unexpected water diuresis emerges during correction, making it difficult to control sodium level and the calculations will be more complicated.

MECHANISMS OF HYPONATREMIA OVERCORRECTION

Hyponatremia overcorrection can occur as a result of excess free water loss, extra sodium load to the extracellular volume or unexpected intracellular free water uptake.

Excessive Free Water Loss

Some factors that cause or maintain hyponatremia, when corrected, allow significant diuresis that leads to a rapid increase in serum sodium concentration in a process known as "autocorrection."[5,10,26,27] This can occur because of eliminating the stimulus for secretion of AVP, for example, by correction of hypovolemia with isotonic saline administration, cessation of nausea after anti-emetics administration[28] or replacement of cortisol in Addison's disease, with resultant water diuresis giving a picture similar to diabetes insipidus. Fraser and Arieff[29]

TABLE 1. Risk factors for the development of ODS

Hyponatremia $>$48 hr
Initial serum sodium $<$105 mEq/L
Development of hypernatremia during treatment
Rapid ($>$0.5 $mEq \cdot L^{-1} \cdot hr^{-1}$) and/or large increase ($>$25 mEq/L per 48 hr) in serum sodium
Severe malnutrition (low blood urea nitrogen)
Alcoholics
Advanced liver disease
Hypokalemia
Hypoxemia
Use of diuretics (especially thiazides)
Cancer
Seizure on presentation