

ACID-BASE AND ELECTROLYTE TEACHING CASE

Treating Profound Hyponatremia: A Strategy for Controlled Correction

Richard H. Sterns, MD, John Kevin Hix, MD, and Stephen Silver, MD

An alcoholic patient presented with profound hyponatremia (serum sodium concentration, 96 mEq/L) caused by the combined effects of a thiazide diuretic, serotonin reuptake inhibitor, beer potomania, and hypovolemia. A computed tomographic scan of the brain was indistinguishable from one obtained 3 weeks earlier when he was normonatremic. Concurrent administration of 3% saline solution and desmopressin controlled the rate of correction to an average of 6 mEq/L daily and resulted in full neurologic recovery without evidence of osmotic demyelination. This case illustrates the value of controlled correction of profound hyponatremia.

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INDEX WORDS: Hyponatremia; desmopressin; antidiuretic hormone; hypertonic saline.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders. Advisory Board member Horacio Adrogué, MD, served as the Consulting Editor for this case. The present case discussion is the second of 2 articles discussing hyponatremia. In this article, Drs Sterns, Hix, and Silver present their approach to the treatment of hyponatremia; in the first teaching case, Drs Berl and Rastegar describe a physiologic-based approach to its diagnosis and evaluation.¹

INTRODUCTION

A serum sodium concentration <100 mEq/L strikes fear in the heart of the most seasoned nephrologist, and for good reason: “double-digit hyponatremia” carries a high risk of brain damage. Although it is appropriate to worry about the consequences of an untreated electrolyte disturbance this severe (seizures and aspi-

ration, falls and fractures, and even death), there is equally valid concern about iatrogenic injury from overcorrection of hyponatremia.

Published reports of osmotic demyelination syndrome (also known as pontine and extrapontine myelinolysis) include many patients who initially presented with moderate symptoms associated with double-digit hyponatremia and then deteriorated neurologically after serum sodium concentrations were increased to seemingly “safer” levels >120 mEq/L.¹⁻⁸

Because the causes of hyponatremia often are reversible when serum sodium concentration decreases to extremely low levels and survival with profound hyponatremia is dependent on adaptations that limit brain cell swelling, such patients are vulnerable to brain injury caused by unintentional overcorrection. Appropriate management can prevent this complication.

CASE REPORT

Clinical History and Initial Laboratory Data

A 45-year-old man with a history of alcoholism (1/2 bottle of vodka and 15-24 cans of beer daily) with recurrent alcohol withdrawal seizures and delirium was found unresponsive in his apartment. Treatment had been started with a thiazide diuretic for hypertension and a selective serotonin reuptake inhibitor (SSRI) for depression 2 weeks earlier after discharge from the hospital for an alcohol withdrawal seizure. On arrival at the emergency department, he was combative and disoriented, requiring sedation. Serum sodium concentration was 96 mEq/L (96 mmol/L), and other laboratory data are listed in Table 1.

On an admission 3 years earlier, the patient had presented with a serum sodium concentration of 115 mEq/L (115 mmol/L; his only prior episode of hyponatremia) shortly after beginning SSRI therapy. Urine osmolality at that time

From Rochester General Hospital, Nephrology Division, University of Rochester School of Medicine and Dentistry, Rochester, NY.

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Address correspondence to Richard H. Sterns, MD, 1425 Portland Ave, Rochester, NY 14621. E-mail: richard.sterns@rochestergeneral.org

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Table 1. Admission Laboratory Data

Parameter	Value
Plasma values	
Sodium (mEq/L)	96
Potassium (mEq/L) ^a	3.5
Chloride (mEq/L)	56
Bicarbonate (mEq/L)	26
SUN (mg/dL)	9
Creatinine (mg/dL)	1.0
Glucose (mg/dL)	119
Osmolality (mOsm/kg)	203
Albumin (g/dL)	4.2
Total bilirubin (mg/dL)	2.5
AST (U/L)	599
ALT (U/L)	218
Creatine kinase (U/L)	19,785
Blood alcohol	Undetectable
Urine values	
Osmolality (mOsm/kg)	732
Sodium (mEq/L)	7

Note: Conversion factors for units: SUN in mg/dL to mmol/L, $\times 0.357$; serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; glucose in mg/dL to mmol/L, $\times 0.05551$; albumin in g/dL to g/L, $\times 10$; bilirubin in mg/dL to $\mu\text{mol/L}$, $\times 17.1$. No conversion necessary for sodium, potassium, chloride, and bicarbonate in mEq/L and mmol/L and for osmolality in mOsm/kg and mmol/kg.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUN, serum urea nitrogen.

^aRepeated serum potassium level 4 hours after admission was 2.4 mEq/L.

had decreased to 70 mOsm/kg with urine output of 3,150 mL over 5 hours, prompting administration of desmopressin to arrest the spontaneous water diuresis and prevent rapid correction of hyponatremia.

Additional Investigations

A computed tomographic (CT) scan of the head showed no cerebral edema, with images indistinguishable from a CT scan obtained 3 weeks earlier when the patient was normonatremic.

Diagnosis

Profound hyponatremia caused by the combination of thiazide diuretic, SSRI, beer potomania, alcohol withdrawal, and hypovolemia.

Clinical Follow-up

Knowledge of the patient’s history amplified concern that spontaneous water diuresis could lead to a dangerous and rapid increase in serum sodium levels. To control this risk while simultaneously treating the present life-threatening hyponatremia, it was decided to administer both desmopressin and 3% hypertonic saline solution. A second serum sodium concentration obtained 4 hours after his arrival at the

emergency department and immediately before starting these measures was 98 mEq/L.

The patient was transferred to the intensive care unit, where he was intubated for airway protection and to permit confident administration of sedatives to treat alcohol withdrawal. Desmopressin was administered at 8- and then 6-hour intervals, and serum sodium concentration gradually was corrected with varying doses of 3% saline solution and intravenous potassium (given as hourly infusions of 20 mEq of potassium chloride in 50 mL). Serum sodium concentration increased to 105 mEq/L (9 mEq/L greater than the presenting value of 96 mEq/L), which was maintained for the first 48 hours. It then increased to 119 mEq/L 4 days after admission (Fig 1). The patient recovered without clinical evidence of osmotic demyelination, and at discharge on hospital day 15, magnetic resonance imaging showed no evidence of pontine or extrapontine myelinolysis. On follow-up 2 years later, he was neurologically intact.

DISCUSSION

Our patient presented with a profoundly low serum sodium concentration; serious neurologic symptoms, most likely after an unwitnessed seizure; and several risk factors for developing osmotic demyelination. There was a clear indication to promptly increase serum sodium concentration “enough” (by at least 4-6 mEq/L) without overcorrecting it (by >10 mEq/L in 24 hours and/or 18 mEq/L in 48 hours).^{5,6,9}

The surest way of achieving a prompt increase in serum sodium concentration (thereby decreasing

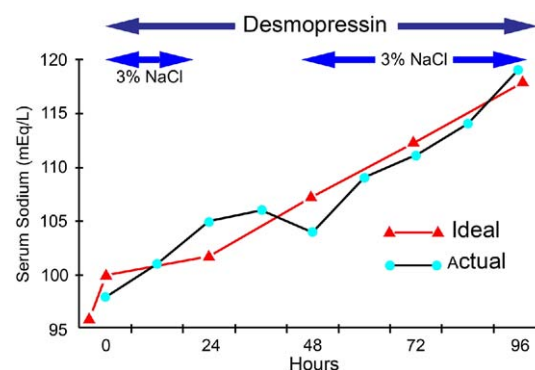


Figure 1. Correction of hyponatremia in the first 4 days. Hypertonic saline solution and desmopressin were administered concurrently 4 hours after the patient’s arrival at the hospital, and desmopressin therapy was continued at 6- to 8-hour intervals after the first hospital day. Between 24 and 48 hours, hypertonic saline solution administration temporarily was discontinued to maintain serum sodium concentration at a level 9-10 mEq/L greater than the admission value of 96 mEq/L. An ideal rate of correction is denoted by the triangles: an initial increase of 4 mEq/L in the first 4 hours and daily correction by 6 mEq/L. No conversion necessary for sodium in mEq/L and mmol/L.

Table 2. Causes of Hyponatremia Associated With Unintentional Overcorrection

Cause of Hyponatremia	Mechanism of Escape From Antidiuresis
Hypovolemia	Volume repletion reverses baroreceptor-mediated vasopressin secretion
Beer potomania, tea and toast diet	Increased solute intake enhances delivery of glomerular filtrate to distal diluting sites
Thiazide diuretics	Discontinuation of diuretic restores diluting function of the distal tubule
SSRI	Discontinuation of antidepressant eliminates drug-induced SIADH
Desmopressin	Discontinuation of synthetic vasopressin eliminates antidiuretic state
Hypopituitarism	Cortisol replacement restores ability to suppress vasopressin secretion
Addison disease	Volume and cortisol replacement
Hypoxemia	Correction of hypoxemia eliminates non-osmotic stimulus for vasopressin
Nausea, surgery, pain, or stress	Spontaneous resolution of SIADH

Abbreviations: SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRI, selective serotonin reuptake inhibitor.

ing the risk of additional seizures) was to administer hypertonic saline solution. However, this therapy carried a high risk of unintentional overcorrection if, as had happened in the past, the cause for water retention was reversible (Table 2).^{10,11} Impaired diluting ability due to a thiazide diuretic and syndrome of inappropriate secretion of antidiuretic hormone caused by an SSRI will resolve soon after these medications are cleared,⁹⁻¹¹ and our patient most likely stopped taking these medications many hours before admission. Similarly, vasopressin secretion in response to hypovolemia ceases when the volume deficit is corrected using saline. Our patient had a very low urine sodium concentration (Table 1), consistent with hypovolemia. Transient vasopressin secretion related to alcohol withdrawal and the stress of a seizure will resolve spontaneously. Our patient had a history of alcohol withdrawal seizures and was delirious despite an undetectable blood alcohol level (Table 1). When nonosmotic stimuli for vasopressin secretion are eliminated,

hypothalamic vasopressin-secreting neurons respond to the low plasma sodium concentration, and plasma vasopressin levels rapidly become undetectable. This results in excretion of up to 1 L/h of maximally dilute urine that will increase serum sodium concentration by >2 mEq/L/h. On a previous admission, this scenario had occurred.

That our patient was alive with a serum sodium concentration this low was a testament to an extraordinary adaptation of his brain to the osmotic disturbance. Brain cells shed organic osmolytes in response to hyponatremia, permitting osmotic equality between intracellular and extracellular fluids without an increase in cell water. This adaptation made the patient vulnerable to iatrogenic injury from aggressive efforts to correct his electrolyte disturbance.¹² The CT scan of the brain, which was indistinguishable from a CT scan obtained 3 weeks previously when his serum sodium level was normal, indicated that there was little risk of herniation. Our initial therapeutic goal was to reduce the likelihood of recurrent seizures with a rapid 5% increase in serum sodium concentration (4 mEq/L).

In a previously published report, we showed that administration of desmopressin is effective in preventing or reversing overcorrection of hyponatremia. We found this to be a more practical strategy than attempting to keep up with unwanted urinary water losses with hypotonic fluids.¹¹ Some patients in our previous study initially presented with hyponatremia caused by the combination of a thiazide diuretic and an SSRI. One of these patients (who also presented with alcohol withdrawal) had experienced spontaneous water diuresis with urine osmolality of 106 mOsm/kg after receiving isotonic saline solution. Her serum sodium concentration increased by 20 mEq/L in 21 hours despite administration of 0.45% saline solution in a failed attempt to prevent overcorrection.¹¹

We were concerned that the unrecognized emergence of water diuresis could rapidly increase serum sodium concentration. Our patient had multiple risk factors for osmotic demyelination syndrome (Box 1), and there have been reports of osmotic demyelination syndrome in patients with alcoholism and liver disease after correction by as little as 10 mEq/L in 24 hours.^{5,9} Therefore, we administered

Box 1. Risk Factors for Osmotic Demyelination Syndrome

- Chronic hyponatremia
- Serum sodium concentration ≤ 105 mEq/L
- Hypokalemia
- Alcoholism
- Malnutrition
- Liver disease

desmopressin without waiting for the emergence of water diuresis. At the same time, hypertonic saline solution administration was begun, which increased the serum sodium concentration from 96 to 100 mEq/L within 12 hours of arrival at the emergency department and within 7 hours of starting 3% saline solution. It might be argued that this initial correction could have been more rapid, but the patient was not having active seizures and his condition had not changed over nearly 4 hours before hypertonic saline solution therapy was begun.

Serum sodium concentration is a function of the body's content of exchangeable sodium and potassium divided by total-body water. The concentration can be increased by administering sodium or potassium (increasing the numerator) or by loss of water (decreasing the denominator; Fig 2).¹ Our strategy was to keep the loss of water constant and low with desmopressin to eliminate one of these variables and to increase serum sodium concentration using hypertonic saline solution and potassium to a level 4-6 mEq/L higher than the admitting value of 96 mEq/L.

During the first 15 hours, the patient was given a total of 570 mL of 513 mmol/L sodium chloride (292 mEq of sodium) and 250 mL of 400 mmol/L potassium chloride (100 mEq of potassium), and net fluid balance was -200 mL. During this time, serum sodium concentration increased from 98 to 105 mEq/L. Assuming body water to be 60 L (60% of his body weight), the increase is almost precisely what would be predicted from the balance data and slightly more than we intended (Fig 2). Our small "overshoot" was caused by our failure to decrease the rate of 3% saline solution infusion during administration of potassium chloride and because the second dose of desmopressin was inadvertently delayed for 15 hours,

resulting in a 50% decrease in urine osmolality and doubling of urine output.

The correction that occurred in our patient was more than our therapeutic target; serum sodium level increased from the admitting value of 96 mEq/L to 105 mEq/L in less than 24 hours. This was perilously close to overcorrection. For this reason, we tried to keep serum sodium concentrations at a stable level for the next 24 hours (Fig 1) before resuming correction at a targeted rate of approximately 6 mEq/L/d.

When desmopressin is administered for the purpose of controlling the rate of correction of hyponatremia, the therapeutic goal differs from the goal in patients with diabetes insipidus.^{9,11,13} In diabetes insipidus, the goal is to allow periodic escape from antidiuresis to prevent hyponatremia. The price for this escape from desmopressin is the mere inconvenience of polyuria. In patients with hyponatremia, the goal is to maintain a constant degree of antidiuresis to make the response to hypertonic saline solution more predictable. In this case, the price for escape from desmopressin is overcorrection. Although "around-the-clock dosing" of desmopressin has advantages, it also has disad-

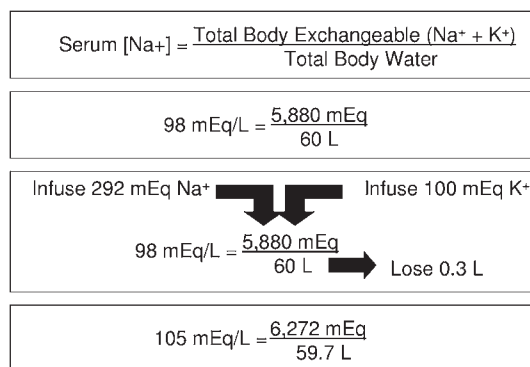


Figure 2. Sodium (Na⁺), potassium (K⁺), and water balance in the first 15 hours of therapy. The observed increase in serum sodium concentration from 98 to 105 mEq/L during the concurrent infusion of 3% sodium chloride, 400 mmol/L of potassium chloride, and desmopressin essentially is identical to the predicted increase based on the amount of sodium and potassium infused (assuming no loss in urine) and overall fluid balance. Total-body water is assumed to be 60% of body weight. The initial value for total-body exchangeable sodium plus potassium (5,880 mEq) is the product of serum sodium concentration at the start of therapy (98 mEq/L) and total-body water (60 L), and the value increases to 6,272 mEq after administration of 292 mEq of sodium and 100 mEq of potassium. No conversion necessary for sodium in mEq/L and mmol/L.

vantages: (1) it prolongs the need for 3% saline solution administration, and (2) it risks inadvertently decreasing serum sodium concentration if the patient takes in water. Water intake and hypotonic intravenous fluids (including those containing medications) must be restricted in hyponatremic patients treated with desmopressin. This strategy is ill advised in patients who are unwilling or unable to restrict their water intake.

In addition to the case reported here and our previously reported case series, there have been a few case reports in which desmopressin was administered with hypotonic fluid to therapeutically re-decrease serum sodium concentration after neurologic findings consistent with osmotic demyelination syndrome had developed.¹⁴⁻¹⁶ One of these patients initially presented with double-digit hyponatremia and fully recovered neurologically.¹⁶

Bolstered by our experience with double-digit hyponatremia, we now routinely manage patients who present with serum sodium concentrations <120 mEq/L with a combination of desmopressin and hypertonic saline (Box 2). A recent review of the literature concluded that correction by 4-6 mEq/L is adequate therapy for the most dire hyponatremic symptoms,⁹ and another

Box 2. Teaching Points for Managing Profound Hyponatremia

- Prompt correction by enough to improve symptoms and reduce the risk of seizures
 - ◊ 4-6 mEq/L is enough correction regardless of the severity of the hyponatremia
 - ◊ Correct hyponatremia rapidly in the first few hours and then slow down
- Limited correction to prevent neurologic injury (osmotic demyelination syndrome)
 - ◊ <10 mEq/L in a 24-hour period
 - ◊ <18 mEq/L in a 48-hour period
 - ◊ Stay well below these limits in patients at high risk of osmotic demyelination
- Anticipate and manage reversible causes of hyponatremia
 - ◊ Administration of desmopressin every 6-8 hours with hypertonic saline solution is an effective strategy to control the rate of correction
 - ◊ Water intake and hypotonic intravenous fluids (including those containing medications) must be restricted in hyponatremic patients treated with desmopressin

Note: No conversion necessary for sodium in mEq/L and mmol/L.

Box 3. Correction Goals for Severe Chronic Hyponatremia

Rule of Sixes:

- Six-a-day makes sense for safety
- Six in six hours for severe sx and *stop*

Explanation:

For all patients with chronic hyponatremia, the goal is 6 mEq/L during the initial 24 hours. For those with severe symptoms (seizure, severe delirium, and unresponsiveness), the goal is preloaded in the first six hours, postponing subsequent efforts to increase serum sodium level until the next day.

Abbreviation: sx, symptom.

widely quoted review concluded on theoretical grounds that increasing serum sodium concentration by 8 mEq/L/d is a reasonable target for correction of chronic hyponatremia.¹⁷ We believe that a 6-mEq/L increase every 24 hours is an appropriate and safe therapeutic target, even in patients with profound hyponatremia (allowing room for a 2-mEq/L unintentional overshoot). This translates to an easy-to-remember “rule of sixes” (outlined in Box 3) to define correction goals (Fig 1). Thus, for all patients with chronic hyponatremia, the correction goal is 6 mEq/L during the initial 24 hours; for those with severe symptoms (seizure, severe delirium, and unresponsiveness), the goal is preloaded in the first 6 hours, postponing subsequent efforts to increase serum sodium level until the next day.

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