



Brain Volume Regulation in Response to Hypo-osmolality and Its Correction

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ABSTRACT

Hyponatremia exerts most of its clinical effects on the brain. An acute onset (usually in <24 hours) of hyponatremia causes severe, and sometimes fatal, cerebral edema. Given time, the brain adapts to hyponatremia, permitting survival despite extraordinarily low serum sodium concentrations. Adaptation to severe hyponatremia is critically dependent on the loss of organic osmolytes from brain cells. These intracellular, osmotically active solutes contribute substantially to the osmolality of cell water and do not adversely affect cell functions when their concentration changes. The adaptation that permits survival in patients with severe, chronic (>48 hours' duration) hyponatremia also makes the brain vulnerable to injury (osmotic demyelination) if the electrolyte disturbance is corrected too rapidly. The reuptake of organic osmolytes after correction of hyponatremia is slower than the loss of organic osmolytes during the adaptation to hyponatremia. Areas of the brain that remain most depleted of organic osmolytes are the most severely injured by rapid correction. The brain's reuptake of myoinositol, one of the most abundant osmolytes, occurs much more rapidly in a uremic environment, and patients with uremia are less susceptible to osmotic demyelination. In an experimental model of chronic hyponatremia, exogenous administration of myoinositol speeds the brain's reuptake of the osmolyte and reduces osmotic demyelination and mortality caused by rapid correction. © 2006 Elsevier Inc. All rights reserved.

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We have known for decades that hyponatremia exerts most of its clinical effects on the brain. A classic series published in 1976 by Arieff and associates¹ showed that lower serum sodium concentrations were correlated with more severe neurologic symptoms, and that the severity of neurologic symptoms and the clinical outcome were markedly affected by the speed of onset of hyponatremia. Patients with acute hyponatremia (defined as <12 hours' duration) had a 29% incidence of seizures and a 50% mortality rate, largely attributable to hyponatremia, whereas patients with chronic hyponatremia (>3 days' duration) had a 4% incidence of seizures and a 6% mortality rate with no deaths attributable to hyponatremia. Subsequent clinical studies have validated

this observation: the likelihood of seizures and coma is much higher in patients who become hyponatremic over the course of hours and such patients may die of cerebral edema, while chronically hyponatremic patients (>2 to 3 days) usually present with more subtle symptoms, and although the mortality rate is high (possibly from the underlying diseases that cause hyponatremia), death from brain herniation is vanishingly rare.

In 1976, Tomlinson and coworkers² reported results in 2 patients with chronic hyponatremia who presented with extraordinarily low serum sodium concentrations (100 mEq/L and 96 mEq/L [1 mEq/L = 1 mmol/L]). The patients' neurologic symptoms were surprisingly modest despite their profound hyponatremia, but they then deteriorated neurologically after treatment with hypertonic saline had increased their serum sodium levels by 32 mEq/L and 35 mEq/L over the course of 1 to 2 days. At autopsy, the

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patients were found to have a recently described demyelinating disorder known as central pontine myelinolysis, with cause unknown.³ The authors speculated on the possible link between hyponatremia and the neurologic injury:

The striking feature in our 2 patients was the gross electrolyte disturbance . . . On admission both patients were drowsy without focal neurological signs, but rapidly deteriorated following attempts to restore the electrolyte imbalance with intravenous saline solutions . . . It is possible that the drowsiness on admission was the result of the hyponatremia and that the electrolyte and osmotic changes resulting from sudden fluid and electrolyte replacement aggravated an already precarious metabolic state in the brain, giving rise to structural damage, with focal neurological signs and deteriorating consciousness.²

This speculation was subsequently confirmed in animal models and observational studies: myelinolysis cannot be induced by uncorrected chronic hyponatremia; rather, the demyelinating lesions are caused by rapid correction of hyponatremia. Hundreds of patients with pontine and extrapontine myelinolysis associated with the rapid treatment of chronic hyponatremia have since been reported in the literature.⁴ Patients who develop such lesions typically exhibit a delayed onset of neurologic symptoms and findings that begin 1 to several days after full or partial correction of their presenting electrolyte disturbance. This clinical course, which has been called the osmotic demyelination syndrome, appears to be preventable, because nearly all patients with chronic hyponatremia who have serum sodium concentrations <105 mEq/L escape without neurologic sequelae if their electrolyte disturbance is corrected more slowly.⁵⁻⁷

These observations lead to 2 important questions: (1) How can patients survive when their serum sodium concentration is ≤ 100 mEq/L? (2) What goes wrong when we try to correct the serum sodium concentration too rapidly? These questions can only be answered with an understanding of how brain volume responds to changes in the serum sodium concentration.

BRAIN VOLUME REGULATION AND THE CONSEQUENCES OF HYPONATREMIA

The osmolality of extracellular and intracellular fluid must be equal. If extracellular osmolality is reduced, cells must either swell with water or rid themselves of solute. Because water is able to cross the blood-brain barrier much more readily than sodium, a low serum sodium concentration osmotically drives water flow into the brain's interstitial space and into brain cells. However, the severity of the induced brain swelling diminishes with time.

Initially, the increase in brain water content is less than what would be expected of a perfect osmometer because of losses of electrolytes from the brain. Sodium chloride is lost within minutes by bulk flow through communications between the brain's interstitial space and the cerebrospinal

fluid. Cellular potassium is lost more gradually, over several hours.

Brain electrolyte content remains relatively constant after these initial losses, and yet the water content of the brain continues to decrease.⁸ The progressive reduction in brain water content over time is explained by loss of organic osmolytes, which we once called *idiogenic osmoles*.⁹⁻¹¹ Organic osmolytes are intracellular, osmotically active solutes that normally contribute substantially to the osmolality of cell water and that do not adversely affect cell functions when their concentrations change.

Organic osmolyte losses from brain cells are comparable in magnitude to cell potassium losses,^{10,11} and there is a strong correlation between the serum sodium concentration and brain organic osmolyte content.⁹ Adaptation to severe hyponatremia is critically dependent on the loss of organic osmolytes from brain cells. When severe hyponatremia is induced in rats over 24 hours, reducing the serum sodium concentration to 96 mEq/L, the combined losses of brain electrolytes and brain organic osmolytes limit the increase in brain water content to a value that is only 4% higher than in normonatremic control animals. If only brain electrolytes had been lost with no loss of organic osmolytes, the increase in brain water content would have been $>10\%$ above normal, a degree of brain swelling that is incompatible with survival.⁹

Similar changes in brain organic osmolyte content have also been documented in humans with hyponatremia using magnetic resonance spectroscopy.^{12,13} Myoinositol is the most prevalent organic osmolyte in the human brain, and its concentration in the brain has been shown to correlate with the level of the serum sodium concentration.

BRAIN COMPOSITION IN ACUTE VERSUS CHRONIC HYPONATREMIA

In animals that have hyponatremia for <24 hours, cerebral edema is severe and rapid correction of hyponatremia returns brain water content to normal with no adverse consequences.⁸ After 3 days of hyponatremia, brain swelling is minimal and brain histology remains normal, even when the serum sodium concentration is maintained at very low levels for several weeks.¹⁴ However, if more sustained hyponatremia is rapidly corrected, the animals deteriorate neurologically and myelinolysis develops.^{8,15-17} Similarly, in humans with acutely developing hyponatremia (e.g., subjects with self-induced water intoxication due to psychosis or marathon running and whose hyponatremia developed in <1 day), rapid correction of hyponatremia improves symptoms, alleviates brain edema, and does not usually cause myelinolysis.¹⁸ In contrast, in patients with chronic hyponatremia whose serum sodium levels are ≤ 105 mEq/L (by definition, patients who become hyponatremic at home drinking conventional amounts of water), correction by ≥ 18 mEq/L over 48 hours leads to transient or permanent neurologic sequelae in approximately 50% of individuals.⁸

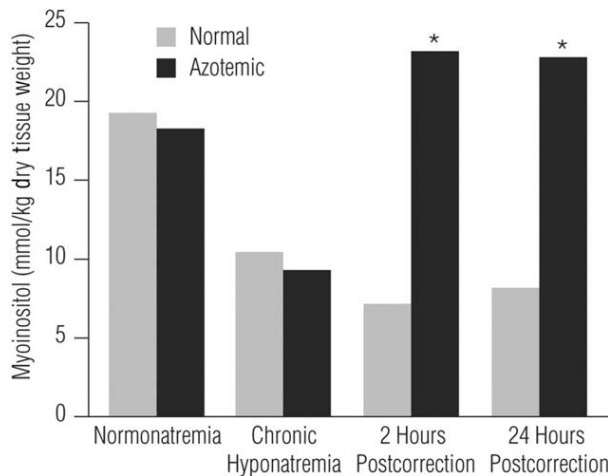


Figure 1 Changes in brain myoinositol in normal and azotemic animals before and 2 or 24 hours after correction of chronic hyponatremia. Postcorrection brain myoinositol content was significantly higher in the azotemic groups (* $P < 0.01$). (Adapted from *J Am Soc Nephrol*.²⁰)

In rats with uncorrected chronic hyponatremia, brain sodium content is low. If the disturbance is corrected rapidly, brain sodium content rapidly increases and an overshoot of brain sodium to supernormal levels occurs.^{8,19,20} Regardless of whether hyponatremia is corrected rapidly or slowly, it takes several days for organic osmolytes to return to the brain.^{10,20,21} The reuptake of organic osmolytes after correction of hyponatremia is slower than is the loss of organic osmolytes during the adaptation to hyponatremia. Similar slow recovery of myoinositol has been shown by magnetic resonance spectroscopy in a human subject with a serum sodium level of 101 mEq/L. Before correction, brain myoinositol was almost undetectable. By 10 days after correction of hyponatremia, brain myoinositol levels were still very low; repeat spectroscopy 2 months later showed a return of brain myoinositol to normal levels.²²

The recovery of organic osmolytes by the brain after the correction of hyponatremia occurs at different rates in different brain regions. Of note, there is an inverse correlation between the regional efficiency of recovering organic osmolytes and the severity of myelinolysis that occurs in that region.²¹

The precise cause of brain injury after rapid correction of hyponatremia is not fully known. However, as experimentally induced myelinolysis is associated with disruption of the blood-brain barrier, shrinkage of endothelial cells may play an important role.^{23,24} Disruption of the blood-brain barrier allows complement components, which are toxic to oligodendrocytes, and other potentially neurotoxic components to enter the brain after rapid correction of hyponatremia.²³ The localization of complement components corresponds to areas of myelinolysis. Other observations suggest that the osmotic insult created by a rapidly increasing serum sodium concentration triggers apoptosis in myelin-producing cells.²⁵

UREA AND MYELINOLYSIS

Intravenous and oral urea are commonly used in Belgium to treat hyponatremia.²⁶ Van Reeth and Decaux²⁷ noted that rapid correction of hyponatremia with urea in an animal model of severe hyponatremia did not appear to cause myelinolysis. Nephrologists know that a rapid increase of the serum sodium concentration is extremely common in patients receiving dialysis, yet myelinolysis in this population is also very rare. Exploring these observations, Soupart and coworkers^{20,28} demonstrated that hyponatremic rats with azotemia tolerated a large increase in serum sodium concentration, whereas the same increase in sodium concentration caused myelinolysis and mortality in nonazotemic animals. As expected, hyponatremic animals without azotemia have low levels of brain sodium and potassium, and an overshoot of brain sodium occurs 24 hours after correction. Azotemic animals, like nonazotemic animals, lose sodium from the brain during the adaptation to hyponatremia; in contrast to nonazotemic animals, however, their brain sodium content does not overshoot after rapid correction of hyponatremia. Uremic and nonuremic animals also differ in their reuptake of brain organic osmolytes after rapid correction of hyponatremia. In uremic animals, substantial reuptake of brain myoinositol, glutamine, taurine, and creatine is found within 2 hours of correction, whereas in the nonazotemic animals no increase in these organic osmolytes is seen. Most remarkably, brain myoinositol content returns to control levels within 2 hours in azotemic animals, whereas nonazotemic hyponatremic animals fail to recover brain myoinositol during this period (Figure 1).²⁰

MYOINOSITOL AND MYELINOLYSIS

If urea protects against injury and this protection is associated with a rapid uptake of brain myoinositol in the brain, can myoinositol be given exogenously to protect against brain injury due to rapid correction of chronic hyponatremia? Studies in our laboratory have shown that hyponatremic animals have brain myoinositol levels that are approximately 50% of those of normonatremic controls. If myoinositol is administered in conjunction with hypertonic saline to hyponatremic animals (increasing the serum sodium by 27 mEq/L), brain myoinositol increases markedly within 3 hours (Figure 2). However, administration of hypertonic saline without myoinositol or administration of myoinositol without hypertonic saline does not increase brain myoinositol content during this period. Thus, exogenous myoinositol enters the brain only if it is given when the serum sodium concentration is increasing.²⁹ More recently, we have shown that exogenous myoinositol improves mortality and reduces the severity of myelinolysis after rapid correction of hyponatremia in rats (Figure 3).³⁰

The mechanism of myoinositol's protective effect remains unknown. Questions for future study include:

- Does the exogenous administration of myoinositol prevent the overshoot of brain sodium that occurs when chronic hyponatremia is rapidly corrected?

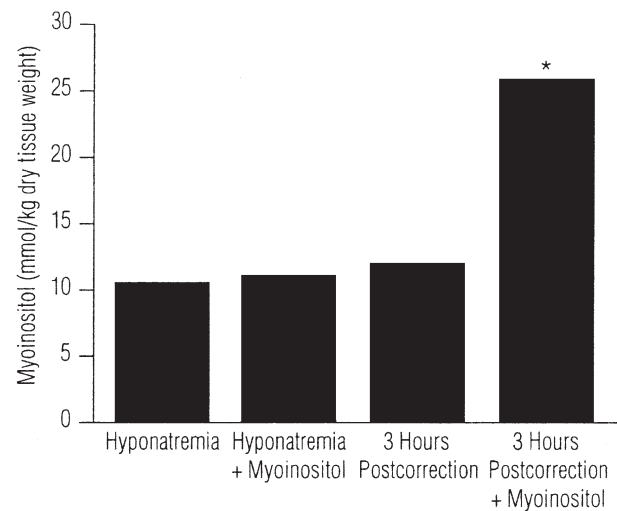


Figure 2 Effect of intravenous administration of myoinositol on brain myoinositol content in chronically hyponatremic animals before and 3 hours after correction. Brain myoinositol content increased in animals infused with myoinositol only when plasma sodium was concomitantly increased (**P* < 0.01 vs. other groups).

- Does myoinositol prevent opening of the blood-brain barrier?
- Does exogenous myoinositol prevent apoptosis?

CLINICAL GUIDELINES

Our knowledge of the brain’s adaptation to hyponatremia can be applied to the bedside. All patients with a serum sodium concentration <120 mEq/L (i.e., >10% below normal) have adapted to some degree because the brain cannot increase its volume by >10% without herniating. The recovery of brain solutes during correction of hyponatremia is

slower than is the loss of brain solutes during the evolution of hyponatremia. Therefore, correction rates should not exceed a 10% increase in sodium concentration (10 to 12 mEq/L in a patient with severe hyponatremia) in any 24-hour period. This physiologically based guideline matches estimates derived from experimental models and clinical observations.^{4–7}

The impulse to return the serum sodium concentration to a level that seems “safe” should be resisted when patients present with extremely severe hyponatremia. Patients with serum sodium concentrations ≤105 mEq/L remain neurologically stable when their serum sodium concentration is allowed to remain <120 mEq/L for 2 days; they may deteriorate neurologically when hyponatremia is corrected to >120 mEq/L within 2 days.⁶ The adaptation to hyponatremia is nearly complete after 48 hours. Patients and animals that have hyponatremia for this long are vulnerable to injury from rapid correction. Therefore, most of the patients we encounter in the clinic have “chronic” hyponatremia and should undergo careful, limited correction.

It must be emphasized that the desire to avoid iatrogenic injury should not deter prompt and even aggressive correction of hyponatremia. Patients who have experienced a rapid decrease in their serum sodium concentration or who are exhibiting severe neurologic symptoms should be treated urgently with hypertonic saline. A 5% increase in sodium concentration is usually all that is needed to stop seizures and eliminate the risk of herniation. An increase of 6 mEq/L in sodium concentration over a few hours is not known to be harmful if subsequent correction over the first 24 to 48 hours of therapy is not excessive. Thus, there is no need to choose between rescuing the patient from life-threatening cerebral edema and preventing brain damage from myelinolysis. Both goals can be achieved.

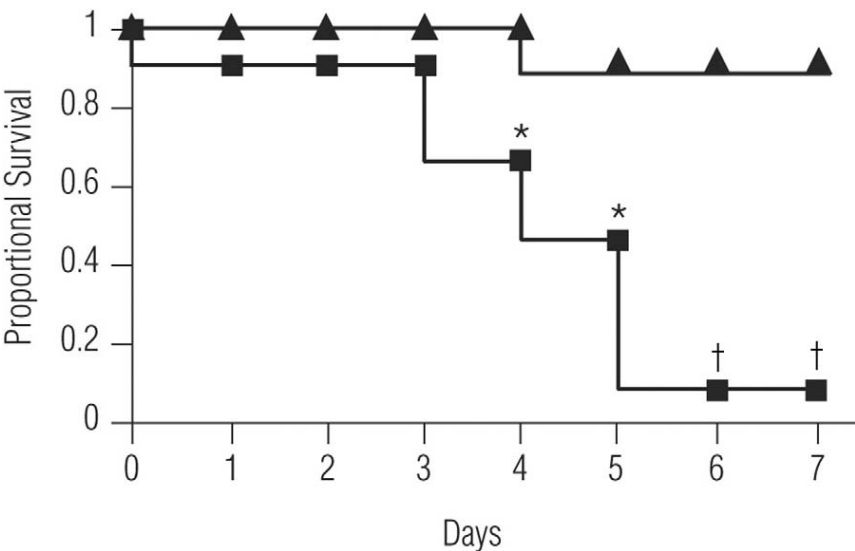


Figure 3 Effect of intravenous administration of myoinositol on survival of rats with chronic hyponatremia undergoing rapid correction of hyponatremia. Myoinositol-treated rats had a significantly greater survival rate than did controls. Triangles = myoinositol-treated rats; squares = control rats. (**P* < 0.05 and †*P* < 0.01 by log rank test). (Adapted from *J Neuropathol Exp Neurol*.³⁰)

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