

The Treatment of Hyponatremia

Richard H. Sterns, MD, Sagar U. Nigwekar, MD, and John Kevin Hix, MD

Summary: Virtually all investigators now agree that self-induced water intoxication, symptomatic hospital-acquired hyponatremia, and hyponatremia associated with intracranial pathology are true emergencies that demand prompt and definitive intervention with hypertonic saline. A 4- to 6-mmol/L increase in serum sodium concentration is adequate in the most seriously ill patients and this is best achieved with bolus infusions of 3% saline. Virtually all investigators now agree that overcorrection of hyponatremia (which we define as 10 mmol/L in 24 hours, 18 mmol/L in 48 hours, and 20 mmol/L in 72 hours) risks iatrogenic brain damage. Appropriate therapy should keep the patient safe from serious complications of hyponatremia while staying well clear of correction rates that risk iatrogenic injury. Accordingly, we suggest therapeutic goals of 6 to 8 mmol/L in 24 hours, 12 to 14 mmol/L in 48 hours, and 14 to 16 mmol/L in 72 hours. Inadvertent overcorrection owing to a water diuresis may complicate any form of therapy, including the newly available vasopressin antagonists. Frequent monitoring of the serum sodium concentration and urine output are mandatory. Administration of desmopressin to terminate an unwanted water diuresis is an effective strategy to avoid or reverse overcorrection.

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For nearly 25 years, the treatment of hyponatremia has been called controversial. The controversy began in the early 1980s with the suggestion that a neurologic disorder called *central pontine myelinolysis* was associated with rapid correction of hyponatremia.¹⁻⁵ About the same time, reports appeared claiming that severe hyponatremia itself was a major cause of brain damage unless it was corrected rapidly.^{6,7} The apparent dilemma led to the joking suggestion that the treatment of hyponatremia must be “unsafe at any speed”⁸ and the more sober concern that clinicians managing the disorder were “damned if they do and damned if they don’t.”⁹ Although some disagreements remain, the past few years have seen the emergence of a general consensus on how acute and chronic hyponatremia can be treated safely and effectively.¹⁰⁻¹⁷

In this review, we first revisit the controversies of the past quarter century to better understand the evidence supporting our current recommendations. We then outline a therapeutic approach to acute and chronic hyponatremia, defining how active, definitive, and effective interventions can be administered while avoiding iatrogenic injury. We define areas where uncertainty (and, of course, some controversy) still remains. Finally, we consider how vasopressin antagonists might be used in the future in a manner that avoids repetition of the mistakes of the past.

HISTORY OF A THERAPEUTIC CONTROVERSY

Acute Water Intoxication and Cerebral Edema

In the 1920s and 1930s, long before measurements of the serum sodium concentration became available to clinicians, it was understood that acute “water intoxication”¹⁸⁻²⁰ could cause fatal cerebral edema and that brain swelling could be reduced and death could be prevented

Department of Medicine, Rochester General Hospital, Rochester, NY; University of Rochester School of Medicine and Dentistry, Rochester, NY.

Address reprint requests to Richard H. Sterns, MD, Rochester General Hospital, 1425 Portland Ave, Rochester, NY 14534. E-mail: Richard.Sterns@Rochestergeneral.org

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Table 1. Acute Versus Chronic Hyponatremia

	Acute	Chronic
Number of patients	14	52
Duration	<12 h	3 d
Serum Na level (mmol/L)	112 ± 2	118 ± 1
Stupor or coma	100%	6%
Seizures	29%	4%
Mortality	50%	6%
Low Na level deaths	36%	0%

Consults at 1 hospital in 1 year; Na <128.
Data from Arieff et al.²²

by the administration of hypertonic saline.¹⁸⁻²⁰ Soon after, it was learned that the brain adapts to hyponatremia with a loss of solute that militates against cerebral edema.²¹ These laboratory observations led to the clinical distinction between acute and chronic hyponatremia; a classic series found that deaths attributable to cerebral edema were limited to patients whose hyponatremia developed over the course of 12 hours, whereas patients who had become hyponatremic over 3 days or more were much less likely to have seizures and did not die from hyponatremia (Table 1).²²

Although it had been known since Helwig et al's¹⁹ first case report in 1935 that acute postoperative hyponatremia could cause death or permanent brain damage from cerebral edema, few such cases could be found in the literature until 1986, when a single-authored case series appeared in the *New England Journal of Medicine*,²³ reporting 15 previously healthy, young women who suffered permanent or fatal brain damage after receiving hypotonic fluids postoperatively. The investigator had not actually been involved in the treatment of these patients, but rather had reviewed cases referred to him from many different hospitals over the course of 15 years; only 3 of the patients had well-documented herniation and 7 patients had a more ambiguous biphasic course, quite different from previous reports of postoperative hyponatremia (see later). Over the next 20 years, deaths and permanent brain damage from postoperative hyponatremia reported by the same investigator escalated to more than 100 cases collected from referrals from all over the country²³⁻²⁸;

most victims were women of childbearing age and young children who presented with seizures, respiratory arrest, and pulmonary edema, and then died shortly afterwards.

In addition to these collected referrals, there have been several single case reports of death from acute hyponatremia caused by hypotonic parenteral fluids or from self-induced water intoxication (most commonly in psychotic patients, marathon runners, and users of ecstasy).²⁹⁻³¹ There should be no doubt that when the serum sodium concentration decreases more rapidly than the brain can adapt to it, patients are at risk for serious complications.

Given the anecdotal nature of the literature on acute hyponatremia, it is uncertain how commonly major morbidity and mortality occurs. For example, a survey of 290,815 surgical procedures on females at the Mayo Clinic from 1976 to 1992 failed to identify any association of respiratory arrest with postoperative hyponatremia, but did identify 6 cases of central pontine myelinolysis.³² Nevertheless, regardless of how commonly it occurs, the fact that some patients rapidly progress from symptoms of drowsiness, disorientation, or delirium to seizures, respiratory arrest, coma, and death has led virtually all investigators to the conclusion that symptomatic acute hyponatremia should be treated urgently with hypertonic saline.

Chronic Hyponatremia and Osmotic Demyelination

Tomlinson³³ was the first to suggest that the treatment of chronic hyponatremia could lead to neurologic injury; he reported 2 women with profound, diuretic-induced hyponatremia (serum sodium level, 96 and 100 mmol/L) but with modest symptoms, who deteriorated neurologically after treatment with 3% saline increased their serum sodium concentration by 25 and 32 mmol/L over 48 hours. At post mortem, the women were found to have central pontine myelinolysis, a disorder first reported in 1959 in alcoholics.³⁴ Tomlinson³³ observed:

The striking feature in our two 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.

Tomlinson³³ also noted that the demyelinating lesions in the patients were not limited to the central pons; similar noninflammatory lesions characterized by destruction of myelin and sparing of neurons also were present in the corticomedullary junction, the claustrum and external capsule, the putamen and caudate head, and the thalamus. Such lesions subsequently were called *extrapontine myelinolysis* in a report, describing neurologic complications in a chronically hyponatremic patient, cowritten by one of the investigators who published the original description of central pontine myelinolysis.³⁵

Shortly after Tomlinson's³³ astute clinical observation, the lesions of central pontine and extrapontine myelinolysis were reproduced in experimental animals by rapidly correcting hyponatremia that had been present for 3 days or more.^{2,3,5} Uncorrected hyponatremia by itself did not cause lesions, and the disorder did not occur in animals with less than 1 day of hyponatremia.³⁶ Concurrently, Norenberg et al,¹ who was also a coauthor of one of the laboratory studies, studied all 12 autopsy-confirmed cases of myelinolysis in their institution, noting that in every patient the symptoms of the disease emerged after an increase in serum sodium concentration of at least 20 mmol/L over the course of 1 to 3 days.

Subsequent clinical and experimental observations by several investigators confirmed these early observations.³⁷⁻⁵² It was learned that an adaptive loss of electrolytes and organic solutes known as *organic osmolytes* protects against life-threatening cerebral edema, even when the serum sodium concentration decreases to the extremely low levels found in Tomlinson's³³

patients.⁵³⁻⁵⁹ This adaptation also makes the brain vulnerable to injury (presumably because of shrinkage of solute-depleted brain cells) if the serum sodium concentration is normalized too rapidly. The brain reclaims organic osmolytes more slowly during correction of hyponatremia than it loses them during the onset of hyponatremia; this slow recovery of osmolytes appears to play an important role in the pathogenesis of iatrogenic brain damage.^{53,56,60} Several lines of evidence in experimental models support this conclusion: (1) brain regions that are most susceptible to myelinolysis are the slowest to reclaim lost osmolytes⁶¹; (2) uremia, which is protective against myelinolysis, is associated with a more rapid recovery of brain organic osmolytes after correction of hyponatremia⁶²; (3) exogenous administration of the organic osmolyte, myoinositol, during correction of hyponatremia rapidly restores brain myoinositol levels and decreases the number and severity of demyelinating lesions in the brain.^{63,64}

The precise mechanism of osmotic demyelination is incompletely understood. It has been suggested that a rapidly increasing serum sodium concentration shrinks brain vascular endothelial cells adapted to chronic hyponatremia, disrupting their tight junctions and opening the blood-brain barrier, allowing circulating complement, cytokines, and lymphocytes to enter the brain, causing oligodendrocyte damage and demyelination.^{44,65,66} Alternatively, oligodendrocytes might be injured directly by shrinkage, triggering apoptosis.^{67,68} Differences in the way that various populations of brain cells respond to osmotic stress may explain why myelin-producing oligodendrocytes are selectively injured by rapid correction of hyponatremia; oligodendrocytes may down-regulate organic osmolyte transporters in response to hyponatremia to a greater extent than other brain cells, making them selectively vulnerable after rapid correction of chronic hyponatremia.^{69,70}

Brain damage associated with rapid correction of chronic hyponatremia presents clinically 1 to 7 days after treatment. The delayed onset of neurologic symptoms has been called *the osmotic demyelination syndrome* because most severely affected individuals who show

these symptoms can be shown to have pontine and extrapontine myelinolysis by magnetic resonance images or autopsy.⁴¹ Magnetic resonance images typically are normal at the onset of symptoms and become positive after approximately 2 weeks.^{50,71}

Patients with the osmotic demyelination syndrome classically present with slowly evolving pseudobulbar palsy and quadriparesis, but symptoms can include movement disorders, behavioral disturbances, or seizures, and in some cases these manifestations can resolve.^{41,50} Hyponatremic patients with alcoholism, liver disease, and malnutrition are particularly susceptible to this complication of therapy, but the disorder can occur in any chronically hyponatremic patient who is subject to a large increase in the serum sodium concentration over the course of one to several days.^{39,52}

Milder, transient, neurologic disturbances lasting only a few days may appear after treatment of hyponatremia in a similar delayed fashion as is seen in patients with demonstrable pontine and extrapontine myelinolysis; the cause of these disturbances may not always be shown by magnetic resonance images.^{45,72} Thus, the osmotic demyelination syndrome was defined clinically (and not anatomically) by its characteristic biphasic presentation after treatment of hyponatremia.⁴¹ Patients with demonstrable pontine and extrapontine myelinolysis are a subset of patients with the osmotic demyelination syndrome.

Anoxic Encephalopathy Versus Osmotic Demyelination

Two articles reporting delayed neurologic deterioration after treatment of hyponatremia appeared in the same issue of the *New England Journal of Medicine*.^{23,41} One said this was an iatrogenic disorder caused by excessive therapy and the other said it was a delayed manifestation of anoxic brain injury. The previously mentioned series of women with postoperative brain damage included 7 patients with a biphasic course: at first, the patients awakened after hyponatremic seizures, appearing to be neurologically intact for a few days before lapsing into an irreversible coma.²³ This led the investigators to conclude that the patients suffered

from delayed postanoxic encephalopathy, a rare disorder that had been described previously among victims of hanging and carbon monoxide poisoning.⁷³ However, the 7 patients had been hyponatremic for more than 48 hours and had been treated with hypertonic saline, increasing their serum sodium concentrations by greater than 25 mmol/L in 48 hours. Magnetic resonance images might have confirmed that these were cases of pontine and extrapontine myelinolysis; however, the technique was unavailable at the time.

Although delayed postanoxic leukoencephalopathy is a biphasic illness, the interval between the hypoxic insult and the onset of delayed neurologic symptoms is considerably longer than the osmotic demyelination syndrome and the disorder has not been known to involve the pons.^{73,74} Subsequent reports of fatal or permanent brain damage in more than 100 women with postoperative hyponatremia by Arieff have documented its association with hypoxia as a result of neurogenic pulmonary edema or hypoventilation, but none of these later cases were said to show the biphasic course that was described in the original report.²⁸

A more recent article by these investigators revisited the role of hypoxia as a cause of brain damage in symptomatic hyponatremia in human beings, citing an extraordinarily high incidence of respiratory arrests, severe hypoxia, death, and severe neurologic sequelae among 53 postmenopausal women with chronic hyponatremia²⁶ (although it should be noted that the investigators' definition of chronic hyponatremia allowed the inclusion of 16 postoperative cases). This is a remarkable finding because in previous work these investigators had found that postmenopausal women were 26 times less likely than menstruant women to die or develop permanent brain damage from acute postoperative hyponatremia²⁴ and because previous work by one of these investigators had reported a favorable prognosis among patients with chronic hyponatremia.²² These unusual findings may reflect the manner in which these patients were identified by the investigators.

The investigators reported an almost uniformly dismal course among 36 postmenopausal women

with symptomatic, chronic hyponatremia who were referred to them for consultation but whose care they had not directed (it is not clear where these patients were treated or why the investigators were consulted); all such cases had experienced respiratory arrests or severe hypoxia ($PO_2 < 50$ mm Hg) requiring endotracheal intubation and mechanical ventilation. The outcome was particularly grim among 14 patients treated with fluid restriction alone; 11 of the 14 patients died, all but one within 24 hours, and 3 patients had documented cerebral edema and evidence of herniation at autopsy. The 22 patients who received treatment with intravenous saline after hypoxia did not die within 24 hours, but 14 were left permanently disabled, vegetative, or dead. We were not told if these patients had a biphasic course, but correction in the 22 cases averaged 30 mmol/L in 41 hours, which, per the investigators, "probably contributed to their brain damage."²⁶

By contrast, the investigators reported a uniformly favorable outcome among 17 postmenopausal women treated promptly with intravenous saline (12 with hypertonic saline) under their guidance, so as to increase the serum sodium by an average of 8 mmol/L within 12 hours and 14 mmol/L within 24 hours (thereby, in their view, avoiding respiratory arrest). These 17 cases included every postmenopausal woman with symptomatic chronic hyponatremia (defined as a plasma sodium level < 130 mmol/L in the presence of central nervous system manifestations such as headache, nausea, emesis, generalized weakness) whose care was directed by the investigators during the interval 1988 to 1997 (an average of 2 patients per year).

The fact that none of the patients actually treated by the investigators experienced pretreatment respiratory arrests or posttreatment neurologic complications is consistent with case series that are free of selection bias. For example, among 223 patients hospitalized for symptomatic hyponatremia (serum sodium level, 98-128 mmol/L) caused by thiazide diuretics in a single hospital in China, no patient died, only 2 patients developed seizures, there were no cases of noncardiogenic pulmonary edema or coma, and only 1 patient developed permanent

neurologic sequelae (a patient with central pontine myelinolysis)⁷⁵; 98% of the patients were managed without hypertonic saline and the average correction in 24 hours was 3 mmol/L (personal communication from KM Chow). Similarly, a prospective series of 184 patients with symptomatic hyponatremia, representing all admitted patients with serum sodium concentrations less than 120 mmol/L (79% of them chronic), reported favorable outcomes with very conservative management. Only 1% of the patients were given hypertonic saline, 24% were treated with fluid restriction alone, and 23% received no therapy; there were no complications among 35 patients corrected by 4 mmol/L or less in 24 hours.⁴⁷

Animal models show that hypoxia exacerbates brain swelling in acute hyponatremia.⁷⁶⁻⁷⁸ Theoretically, hypoxia related to hyponatremia-induced seizures, neurogenic pulmonary edema, or aspiration could trigger a vicious cycle culminating in herniation. However, despite claims to the contrary, attempts to induce myelinolysis in experimental models have not been successful. Animals with severe hyponatremia do not become spontaneously hypoxic⁷⁹ and exposure of hyponatremic animals to hypoxia is uniformly fatal.⁷⁷ Exposure of *normonatremic* animals to severe hypoxia induces brain lesions with a similar distribution to those associated with rapidly corrected hyponatremia, but unlike the lesions of myelinolysis, which are characterized by selective damage to oligodendrocytes, the hypoxic lesions affect neurons.⁷⁷

In a series of 14 patients with documented pontine and extrapontine myelinolysis complicating the treatment of hyponatremia, no patient had a hypoxic episode before the onset of the neurologic manifestations of their disease, and only 2 had experienced hyponatremic seizures (without accompanying hypoxia).³⁹

Is Brain Damage in Chronic Hyponatremia Caused by Slow or Delayed Treatment?

At the same time that reports of myelinolysis complicating hyponatremia were first appearing in the neurologic literature, an important series was published suggesting that delayed or inadequate treatment of chronic diuretic-in-

duced chronic hyponatremia could lead to brain damage in outpatients.⁶ The 5 patients reported in this series presented with serum sodium concentrations ranging from 98 to 105 mmol/L; although their ultimate outcome (paralysis in 2 and coma in 3 cases) was attributed to the profound hyponatremia, each had been treated eventually with hypertonic saline, resulting in correction ranging from 25 to 32 mmol/L within 48 hours. Therefore, although there was no autopsy confirmation of the nature of neurologic injury, these cases had much in common with the cases reported by Tomlinson.³³

In the early 1980s, a controversy emerged in the literature, as to whether rapid or slow correction was the better therapy for severe, symptomatic hyponatremia. Accordingly, opposing viewpoints on the treatment of hyponatremia appeared in a book titled "Controversies in Nephrology and Hypertension," published in 1984.^{80,81} The advocates of rapid correction found the evidence linking central pontine myelinolysis with the treatment of hyponatremia to be unconvincing and offered a literature review purporting to show that the prognosis of symptomatic hyponatremia was greatly improved by more rapid rates of correction.⁸⁰ According to the review, among nonalcoholic patients with serum sodium concentrations averaging 111 mmol/L, survival was 93% in patients treated rapidly (1.9 ± 0.7 mmol/L/h) versus 58% in patients treated slowly (<0.7 mmol/L/h). The same analysis was featured in a subsequent, widely quoted editorial.⁸² The investigators dismissed the previously mentioned patients reported by Tomlinson³³ as victims of profound hyponatremia, citing mortality rates of 63% in nonalcoholics and 86% in alcoholic subjects with serum sodium concentrations less than 105 mmol/L.

However, these conclusions were challenged in contemporaneous literature reviews. Among 80 reported patients with serum sodium concentrations of 105 mmol/L or less, a 1986 review found 51 patients with sufficient data to analyze treatment and outcome: more than half of the 38 patients corrected by more than 12 mmol/L/d experienced posttherapeutic neurologic deterioration, 14 of them with docu-

mented or suspected central pontine myelinolysis; in contrast, all 13 patients corrected by less than 12 mmol/L/d, including 9 patients treated with water restriction only, enjoyed an uncomplicated recovery.⁴¹

A 5-year study of patients admitted to 2 teaching hospitals in Rochester, New York, found that literature reviews exaggerate the true morbidity and mortality rates associated with serum sodium concentrations of 105 mmol/L or less and it did not support the idea that rapid rates of correction were needed to ensure survival.⁸³ Only 1 of 19 patients died, an alcoholic who developed central pontine myelinolysis after treatment with hypertonic saline.

Although the mortality rate was not high in this series, posttherapeutic neurologic complications were frequent among patients with serum sodium concentrations of 105 mmol/L or less—but only among those with chronic hyponatremia. Four of 7 chronically hyponatremic patients deteriorated neurologically after correction to 120 mmol/L by a rate averaging greater than 0.55 mmol/L/h. Eight patients (including one with hospital-acquired hyponatremia) with serum sodium concentrations of 105 mmol/L or less enjoyed uneventful recoveries after slower rates of correction ranging from 0.21 to 0.55 mmol/L/h. As discussed later, these observations subsequently were confirmed in a larger multicenter series of patients with serum sodium concentrations of 105 mmol/L or less.⁴⁵

In the Rochester series,⁸³ calculation of the rate of correction was based on the time required to reach a serum sodium concentration of 120 mmol/L. If the rate of correction had been calculated from the time required to increase the serum sodium level to 128 mmol/L (as it was in the "Controversies in Nephrology and Hypertension" literature review⁸⁰), all 4 patients with neurologic complications would have been misleadingly classified as victims of slow correction. In the patient with fatal central pontine myelinolysis, the average rate of correction to a target of 128 mmol/L was 0.34 mmol/L/h, a calculation that obscures the fact that the serum sodium concentration was increased by 15 mmol/L over 5 hours (3 mmol/L/h) during an infusion of 3% saline and by greater than 25 mmol/L within 48 hours. Simi-

larly, in the “Controversies” review,⁸⁰ most deaths attributed to slow correction were in patients with documented central pontine myelinolysis (including the 2 patients reported by Tomlinson³³) who had experienced increases in serum sodium concentration exceeding 25 mmol/L in 48 hours.

Tolerance of Rapid Correction

Large, rapid increases in the serum sodium concentration do not always cause neurologic complications. One widely quoted series reported good outcomes in 33 patients with symptomatic hyponatremia who were treated with hypertonic saline, increasing the serum sodium at a rate of 1.3 ± 0.2 mmol/L/h over 17 ± 1 hours.⁸⁴ In 5 of these patients, hyponatremia was corrected over 4 to 9 hours at rates ranging from 1.6 to 4.7 mmol/L/h. However, it is unclear how many of these patients had hospital-acquired hyponatremia, how many had community-acquired hyponatremia, how many had self-induced water intoxication, and how many had mild hyponatremia; we were only told that 30 of the 33 patients had been hyponatremic for more than 24 hours and that 3 of the patients had severe hyponatremia caused by glycine absorption during prostate surgery (a hyperacute disorder that is biologically distinct from hypotonic hyponatremia⁸⁵).

Patients and animals with acute hyponatremia usually tolerate rates of correction that are harmful in chronic hyponatremia. Because the true duration of hyponatremia is difficult to establish, we have operationally defined patients who become hyponatremic at home drinking conventional amounts of fluid as having *chronic hyponatremia* and patients with self-induced water intoxication (as a result of psychosis, ecstasy use, or marathon running) and patients with hospital-acquired hyponatremia as having *acute hyponatremia*. By using these definitions, 2 observational studies of patients with severe symptomatic hyponatremia were able to show that acutely hyponatremic patients did well after correction rates exceeding 1 mmol/L/h whereas chronically hyponatremic patients often developed posttherapeutic neurologic complications after correction to greater than 120 mmol/L at rates greater than 0.55 mmol/L/

h.^{45,83} Similar conclusions were supported in a review of the literature.⁸⁶

Magnitude Versus Rate of Correction

When an association between the treatment of hyponatremia and myelinolysis was first proposed, *rapid correction* was defined as an increase of 20 mmol/L over 1 to 3 days.¹ Subsequently, a definition of greater than 12 mmol/L/d was used to define *rapid correction*.⁴¹ Unfortunately, in the ensuing debate, correction rates often were expressed in mmol/L/h. Thus, patients with mild, chronic hyponatremia whose serum sodium concentrations were increased rapidly (defined as >0.7 mmol/L/h) by less than 12 mmol/L in 24 hours were cited as evidence that rapid correction of hyponatremia is not harmful.^{84,87} It then was asserted that the rate of correction of hyponatremia is irrelevant but the magnitude of correction is an important risk factor for the development of demyelinating brain lesions; based primarily on an analysis of autopsy-proven cases of myelinolysis, it was suggested that the magnitude of correction (or delta) not exceed 25 mmol/L in 48 hours.⁸⁴ It should be apparent that mmol/L/h, mmol/L/d, and mmol/L/48 h are simply different ways of expressing the rate of correction.

APPROACHING CONSENSUS: OUR RECOMMENDATIONS

Acute or Severely Symptomatic Hyponatremia

Self-induced water intoxication and symptomatic hospital-acquired hyponatremia are true hyponatremic emergencies that demand prompt and definitive intervention with hypertonic saline. In these conditions, the risks of the electrolyte disturbance itself exceed the risks of excessive therapy and fear of osmotic demyelination should not deter aggressive treatment. Because minor degrees of cerebral edema can be catastrophic in patients with increased intracranial pressure caused by underlying neurologic or neurosurgical disease, similar recommendations apply to patients with intracranial hemorrhage, brain tumors, or central nervous infections who become hyponatremic. There is a risk that the serum sodium concentration may

Table 2. Patients With Hyponatremic Seizures, Coma, or Cerebral Edema Treated With Hypertonic Saline (Serum Sodium Level at < 4 Hours)

Study	Etiology	Age/ Sex	Seizure	Cerebral Edema	Initial Sodium Level, mmol/L	Post- Treatment Sodium Level, mmol/L	Time Between Laboratory Values, h	Outcome
Worthley and Thomas ⁹⁴	Postoperative	65 M	Yes	Unknown	109	116	0.5	Recovered
Worthley and Thomas ⁹⁴	Postoperative	47 F	Yes	Unknown	109	117	0.5	Disabled*
Worthley and Thomas ⁹⁴	Postoperative	28 F	Yes	Unknown	100	109	0.5	Recovered
Worthley and Thomas ⁹⁴	Burns	45 M	Yes	Unknown	106	112	0.5	Recovered
Worthley and Thomas ⁹⁴	Psychosis/ polydipsia	67 F	Yes	Unknown	99	106	0.5	Recovered
Drescher et al ⁹⁵	Psychosis/ polydipsia	63 F	Yes	Unknown	100	108	1	Recovered
Snell and Bartley ⁹¹	Hypoadrenal/ polydipsia	25 M	Yes	No	111	117	3.6	ODS/recovered†
Goudie et al ⁹⁸	Runner	31 F	Yes	Unknown	116	121	2	Recovered
Hew-Butler et al ⁹⁹	Runner	47 M	Yes	Unknown	112	116	1	Recovered
Rae ⁹⁰	Psychosis/ polydipsia	53 F	Yes	Unknown	117	124	2	Recovered
Schreiber et al ⁹²	Postoperative/ DDAVP	50 F	No	Yes	111	116	4	Recovered
Speedy et al ⁹⁶	Runner	35 M	Yes	No	116	122	4	Recovered
Fisher et al ¹⁰⁰	SSRI (outpatient)	92 F	Yes	Yes	109	112	4	Recovered

Abbreviations: ODS, osmotic demyelination syndrome; DDAVP, desmopressin; SSRI, selective serotonin reuptake inhibitor.

*Given additional 90-mL bolus of 29.2% saline after resolution of seizures; 31-mmol/L increase in serum sodium level over 8 hours.

†Water diuresis after adrenal replacement; 28-mmol/L increase in serum sodium level in 42 hours.

decrease spontaneously unless hypertonic saline is administered: in acute water intoxication there may be delayed absorption of water from the gastrointestinal tract⁸⁸; in patients with the syndrome of inappropriate antidiuresis who have received parenteral fluids, excretion of highly concentrated urine converts infused isotonic fluids to free water.⁸⁹

How much correction is required for a hyponatremic emergency? Many investigators have recommended correction of acute hyponatremia by 1 to 2 mmol/L/h, basing their recommendation on case series reporting favorable outcomes.⁸⁴ However, as discussed earlier, hourly rates of correction reported in the literature usually are average rates calculated from a beginning serum sodium concentration to an arbitrary target reached many hours later; such calculations obscure the initial rate of correction in the critical first hour or two of therapy.

We reviewed the literature to identify reports of hyponatremic patients with seizures or coma in whom data on correction within the first 4 hours were provided⁹⁰⁻¹⁰⁰ (Table 2). The data suggest that a 4- to 6-mmol/L increase in serum sodium concentration is enough. One series reported on 5 patients with active hyponatremic seizures given 50-mL infusions of 29.2% saline over 10 minutes (the equivalent of 487 mL of 3% saline), increasing the serum sodium concentration by 7 to 9 mmol/L; the investigator mentions that seizures stopped during the infusions, in one case after the first 5 minutes, suggesting that a smaller volume might have been equally effective.⁹¹ In many of these cases, correction continued after the first few hours; although large, 24-hour increases in sodium concentration usually (but not always) are tolerated in acute hyponatremia, there is no evidence that such increases are necessary.

Hypertonic saline solutions have emerged as a preferable alternative to mannitol to treat increased intracranial pressure (ICP) in normonatremic patients with neurosurgical conditions. We can draw on recent experience treating cerebral edema in normonatremic subjects to better define optimal treatment for critically ill patients with hyponatremia. A 4-year, single-center study of 63 normonatremic patients treated for transtentorial herniation (caused by a variety of neurosurgical conditions) found that a 30-mL bolus of 23.4% saline, increasing the serum sodium level by 5 mmol/L, causes a prompt reversal of clinical signs of herniation and nearly a 50% reduction in intracranial pressure within 1 hour.¹⁰¹ The 30-mL bolus of 23.4% saline used in this study is equivalent in sodium content to 240 mL of 3% saline. Infusion of a larger dose of 23.4% saline (2 mL/kg) to patients with subarachnoid hemorrhage, increasing the serum sodium level by 11.2 ± 4.0 mmol/L at 1 hour, significantly increased cerebral perfusion pressure and decreased ICP by 93%, in some cases to levels below 0 mm Hg, suggesting excessive shrinkage of the intracranial contents. In a placebo-controlled study of patients with subarachnoid hemorrhage, infusion of 2 mL/kg of 7.2% saline, increasing the serum sodium by 4 to 7 mmol/L at 30 minutes and 1 to 5 mmol/L after 210 minutes, was sufficient to decrease ICP and increase cerebral perfusion pressure.^{102,103} Based on these findings and a review of other published observations, the investigators would now recommend that the initial bolus be less than 2 mL/kg of the 7% solution (equivalent to <4.7 mL/kg of a 3% saline solution).

The Second International Exercise-Associated Hyponatremia Consensus Development Conference recommended that any athlete with hyponatremia and encephalopathy should be treated immediately with a bolus infusion of 100 mL of 3% NaCl to acutely reduce brain edema, with up to 2 additional 100-mL 3% NaCl bolus infusions that should be given at 10-minute intervals if there is no clinical improvement.¹⁰ We believe that this is a reasonable regimen for all symptomatic patients with acute hyponatremia, for hyponatremia associated with underlying neurologic or neurosurgical conditions, and for

all hyponatremic patients with seizures or coma regardless of the duration of the electrolyte disturbance. This regimen translates to a maximum of 6 mL/kg of 3% saline in a 50-kg woman, enough to increase the serum sodium concentration by 5 to 6 mmol/L. Once the bolus therapy has been completed, further treatment with hypertonic saline may be unnecessary.

Chronic Hyponatremia

Virtually all investigators now agree that overcorrection of hyponatremia risks iatrogenic brain damage, even if they cannot agree on what to call it. Although rejecting the terms *myelinolysis* and *osmotic demyelination* and denying the validity of a correction limit of 12 mmol/L in 24 hours, one well-published group allowed that correction by 25 mmol/L or greater in 48 hours is excessive and “might” be a factor in causing “cerebral demyelinating lesions.”⁸⁴ A multicenter study of patients with serum sodium concentrations of 105 mmol/L or less confirmed that a 2-day definition of overcorrection best divided patients with posttherapeutic neurologic complications from patients with an uncomplicated course.⁴⁵ However, because correction rates between 18 and 25 mmol/L in 48 hours sometimes led to complications, the 2-day limit was set at 18 mmol/L; more than half the patients whose correction exceeded this limit experienced posttherapeutic neurologic events whereas all patients corrected more slowly had an uncomplicated recovery. Recently, Ayus, one of the investigators¹⁴ who first proposed the limit of 25 mmol/L in 48 hours appears to have heeded these observations, recommending that correction not exceed 15 to 20 mmol/L in the first 48 hours. Similarly, the originally proposed 1-day limit of 12 mmol/L may need revision. Two case series and a few case reports have identified patients with pontine and extrapontine myelinolysis after correction by only 10 mmol/L in 24 hours.^{39,47,104-106}

No therapeutic limit is absolutely safe. These guidelines were derived from relatively small numbers of patients and they can only give us a rough estimate of correction rates associated with an unacceptable risk of harm. Based on what is now known, we suggest the following

limits: 10 mmol/L in 24 hours, 18 mmol/L in 48 hours, and 20 mmol/L in 72 hours. These should be regarded as limits not to be exceeded rather than therapeutic goals. The goal of therapy should be adequate to keep patients safe from serious complications of hyponatremia while staying well clear of correction rates that risk iatrogenic injury. Accordingly, we suggest a goal of 6 to 8 mmol/L in 24 hours, 12 to 14 mmol/L in 48 hours, and 14 to 16 mmol/L in 72 hours. For patients with advanced liver disease or severe malnutrition who are at very high risk for osmotic demyelination, even slower daily rates of correction are indicated.^{107,108}

Avoiding Undercorrection

Chronic hyponatremia usually causes moderate but distressing symptoms (eg, weakness, confusion, delirium, gait disturbances, muscle cramps, nausea, and vomiting) that deserve treatment.^{47,75} Although infrequent, seizures can occur in patients with extremely low serum sodium concentrations, pre-existing seizure disorders, or alcohol withdrawal. Even apparently asymptomatic, mild chronic hyponatremia causes demonstrable gait disturbances and disturbed cognition, and it is associated with a markedly increased risk of falls and fractures.^{109,110} Therefore, therapeutic measures that reliably increase the serum sodium concentration should be implemented in every patient with hyponatremia.

Unless the patient is excreting a maximally dilute urine, fluid restriction is a needed adjunct to therapy. However, in some patients who lack a reversible cause for water retention, fluid restriction alone will increase the serum sodium concentration by little more than 1 to 2 mmol/L per 24 hours. If urine chemistries are available, the concentration of cations in the urine divided by the plasma sodium concentration can help predict the response to therapy.¹¹¹ If the ratio is less than 0.5, the urine is more than half electrolyte-free water; in this case, correction of hyponatremia can be expected to be prompt (and sometimes faster than intended) and fluid restriction need not be stringent. Conversely, when the ratio is equal to or greater than 1.0, the urine contains no electrolyte-free water; hyponatremia can be expected to be recalci-

trant to therapy unless water intake is limited severely, or the concentration of urinary electrolytes is reduced (eg, with furosemide), or hypertonic saline is administered.

If the patient is hypokalemic, administration of potassium will help increase the serum sodium concentration. The serum sodium concentration is a function of exchangeable sodium plus exchangeable potassium divided by total body water¹¹²; therefore, each millimole of potassium added to the body can be expected to increase the serum sodium concentration as much as a mmol of added sodium.¹¹³ There is a limited published experience validating this expectation in patients with diuretic-induced hyponatremia,¹¹⁴ and in our experience (unpublished observations), potassium effectively corrects hyponatremia regardless of the cause of potassium depletion. Hourly intravenous infusions of 10 mmol of KCl in 100 mL 0.9% NaCl are effective therapy for hyponatremia in potassium-depleted patients. The solution has a total cation concentration of 254 mmol/L, high enough to exceed the urine cation concentration in virtually all patients; therefore, similar to hypertonic saline, it can be relied on to increase the serum sodium concentration.

Isotonic saline is effective in correcting hyponatremia caused by volume depletion because the elimination of a volume stimulus for vasopressin secretion results in a water diuresis. However, if vasopressin is secreted for other reasons (as in patients with the syndrome of inappropriate antidiuretic hormone secretion [SIADH] caused by nausea, pain, surgical stress, respiratory infections, tumors, neurologic conditions, or medications), isotonic saline is ineffective. If the urine cation concentration is much higher than 154 mmol/L, the serum sodium concentration may actually decrease during the infusion of isotonic saline. The sodium contained in a liter of saline is excreted in less than 1 L of urine, “desalinating” the infused saline; the net effect is free water retention.⁸⁹ Therefore, we reserve isotonic saline for hyponatremic patients who require volume resuscitation for hypotension or patients with mild hyponatremia who are not at risk if the serum sodium concentration fails to improve with this therapy.

In our experience, many hospitalized patients present with multiple conditions that are potential causes for hyponatremia.¹¹⁵ Although urine chemistries can help predict the response to isotonic saline, these laboratory results are not always available to guide therapeutic decision making. Therefore, we often initiate therapy with hypertonic saline because it will increase the serum sodium concentration reliably regardless of etiology. An infusion of 3% saline at 15 to 30 mL/h can be used for chronically hyponatremic patients who are neither seizing nor comatose.^{116,117} Chemistries should be obtained at 4- to 6-hour intervals during the infusion and the urine output should be monitored carefully. Hypertonic saline should be discontinued after the serum sodium level has increased by 4 to 6 mmol/L or if a water diuresis emerges.

Inadvertent Overcorrection

We discourage the use of formulas to predict the increase in serum sodium concentration. A number of conditions temporarily or reversibly impair water excretion. Once the impairment resolves, excretion of dilute urine increases the serum sodium concentration by much more than would be predicted by calculations that ignore urine output.^{116,118,119} There are several settings in which this can occur: (1) volume resuscitation in patients with excess vasopressin caused by hypovolemia or low solute intakes (eg, beer potomania); (2) discontinuation of thiazide diuretics, or drugs causing the syndrome of inappropriate antidiuresis; (3) cortisol replacement in patients with adrenal insufficiency; and (4) spontaneous resolution of a reversible cause of the syndrome of inappropriate antidiuresis, such as nausea, hypoxia, or recent surgery. Once the cause of water retention ends, a spontaneous water diuresis ensues, which may increase the plasma sodium concentration by 2 mmol/L/h or more.

A single-center retrospective study of 62 consecutive hyponatremic patients treated with hypertonic saline showed that despite a low rate of infusion averaging 23.5 mL/h, frequent adjustments in the rate of infusion, and/or administration of 5% dextrose in water as an antidote, the serum sodium concentration often increased

by more than would be predicted and by more than was intended; in 11% of cases, correction exceeded 12 mmol/L in 24 hours and in 10% of cases it exceeded 18 mmol/L in 48 hours.¹²⁰ All of the patients had been treated under the supervision of nephrologists seeking to maintain correction rates within these guidelines. The magnitude of correction was correlated directly with the plasma sodium concentration, with more severe hyponatremia associated with more rapid correction (Fig. 1).

In 74% of patients with a plasma sodium concentration less than 120 mEq/L, the actual increase in plasma sodium concentration exceeded the increase predicted by the popular Adrogue-Madias formula¹²¹; actual correction was as much as 5 times predicted (Fig. 2). In about half the cases, a documented water diuresis could account for the excessive correction. Overcorrection of hyponatremia may complicate any form of therapy for hyponatremia; patients given large volumes of isotonic saline may be more likely to overcorrect than patients given low volumes of hypertonic saline.¹¹⁹

Desmopressin to Correct Overcorrection

In animal models, the incidence and severity of demyelinating brain lesions caused by rapid correction of hyponatremia can be reduced by therapeutically re-lowering the serum sodium concentration.¹²² Consistent with these observations, in single-patient case reports, desmopressin has been used successfully to therapeutically re-lower the serum sodium concentration after inadvertent overcorrection of hyponatremia had resulted in symptoms suggestive of osmotic demyelination.¹²³⁻¹²⁵

A recent report described the use of desmopressin as a therapeutic agent to avoid overcorrection of hyponatremia and to re-lower the plasma sodium concentration after inadvertent overcorrection without waiting for early symptoms of osmotic demyelination.¹¹⁵ Six patients were given desmopressin acetate as a rescue maneuver after the 24-hour limit of 12 mmol/L already had been reached or exceeded; correction was prevented from exceeding the 48-hour limit of 18 mmol/L in 5 of the 6 patients (the patient who was the exception had exceeded the goal before desmopressin was given). Four-

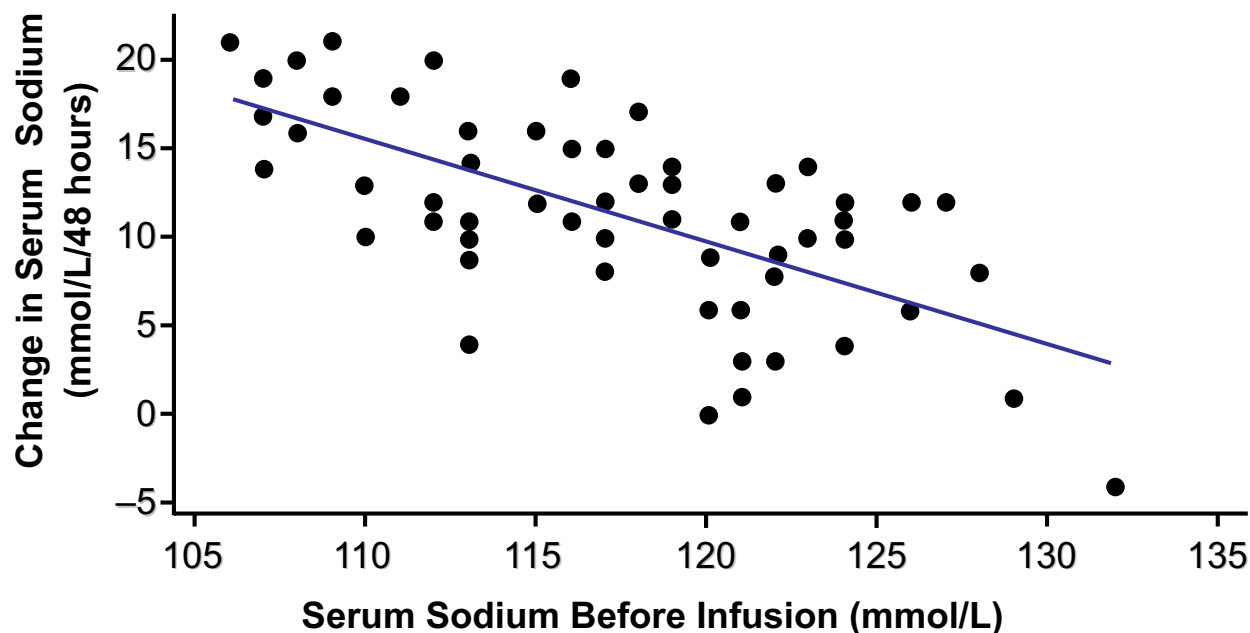


Figure 1. Relationship between the increase in serum sodium concentration during the first 48 hours of therapy and the pre-infusion serum sodium concentration in a series of patients treated with 3% saline. Data from Mohmand et al.¹²⁰

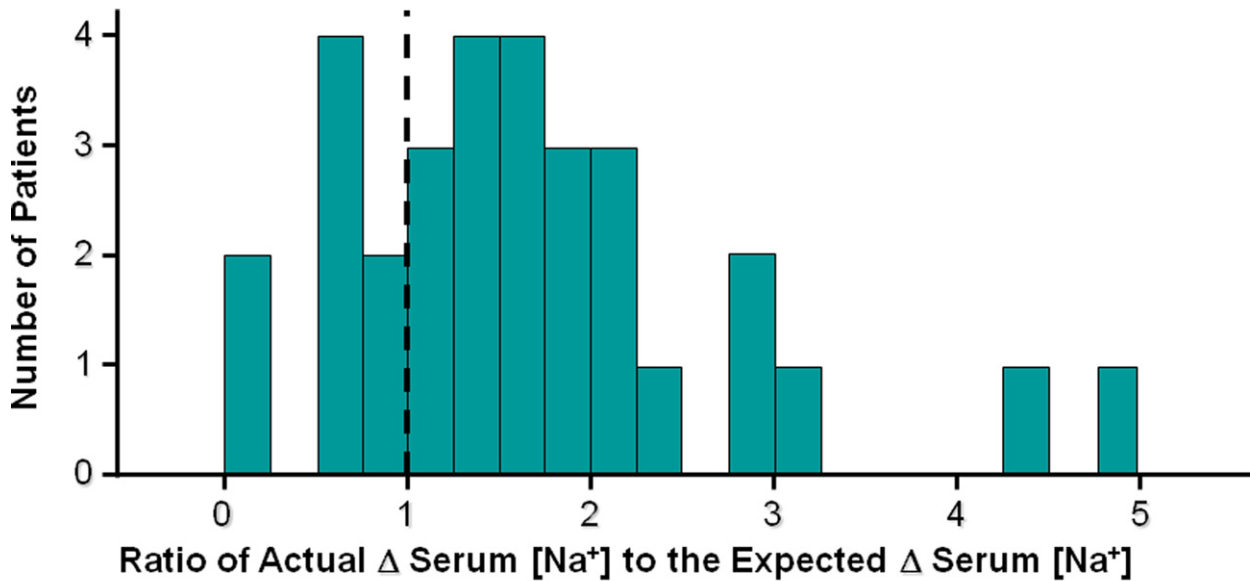
teen patients were given desmopressin acetate in anticipation of overcorrection after the plasma sodium concentration had increased by 1 to 12 mmol/L. In all 14 patients who were treated with desmopressin acetate as a preventive measure, correction was prevented from exceeding either the 24- or 48-hour limits. In all 6 patients treated after overcorrection and in 5 patients treated prophylactically, the plasma sodium concentration was actively re-lowered by 2 to 9 mmol/L with the concurrent administration of desmopressin acetate and 5% dextrose in water; no serious adverse consequences from this maneuver were observed and all patients survived without neurologic sequelae.

The ideal regimen for desmopressin in the management of hyponatremia awaits further study. There is no conclusive evidence that the use of desmopressin is superior to simply giving water to match urine losses; however, many patients in this series were given desmopressin after attempts to match urinary losses had failed. Based on our experience, we give 2 mcg of desmopressin parenterally as soon as the targeted initial increase in serum sodium concentration (\approx 6-8 mmol/L) has been achieved or as soon as a water diuresis is recognized.

If the patient is at risk of overcorrection, the goal of desmopressin administration is to completely prevent or stop a water diuresis; therefore, we recommend beginning with a dosing interval of 6 or 8 hours, rather than the twice-daily dosing schedule used in patients with diabetes insipidus. Less-frequent dosing intervals can be used later in the patient's course to allow water losses to increase the serum sodium concentration further. Alternatively, desmopressin can be continued, maintaining an antidiuresis until the serum sodium concentration has been increased to the mildly hyponatremic range with the concurrent administration of hypertonic saline.

Vasopressin Antagonists

Sustained hypotonic hyponatremia almost always is mediated by vasopressin. Treatment of the electrolyte disturbance with vasopressin antagonists makes sense physiologically and may have advantages over currently available therapy, particularly in patients with hyponatremia associated with heart failure or cirrhosis and patients with hyponatremia caused by irreversible SIADH.¹²⁶ Two distinct vasopressin-receptor subtypes (V_{1A} and V_2) mediate the hor-



$$\text{Expected } \Delta \text{ Serum } [\text{Na}^+] \text{ with 1 L infusate} = \frac{\text{Infusate } [\text{Na}^+] - [\text{Na}^+]}{\text{Total Body Water} + 1}$$

Figure 2. Ratio of actual to expected increase in sodium as calculated using the Adrogue-Madias formula.¹²¹ A value of 1 indicates that the observed increase in serum sodium concentration after hypertonic saline (actual Δ serum $[\text{Na}^+]$) equals the increase in serum sodium predicted by the formula (expected Δ serum $[\text{Na}^+]$). Values greater than 1 indicate that the actual increase exceeded the predicted increase in most patients. Data from Mohmand et al.¹²⁰

none's major physiologic effects. V_{1A} receptors are located on vascular smooth muscle cells and cardiomyocytes, affecting vascular tone and myocardial function. V_2 receptors are located on renal collecting duct principal cells, coupled to vasopressin-sensitive water channels that promote the reabsorption of water in the cortical and medullary collecting duct. Blockade of V_2 receptors causes an aquaresis, the excretion of increased volumes of dilute urine without an increase in sodium or potassium excretion.

Conivaptan, which blocks both V_2 receptors and V_{1A} receptors, is currently the only drug of its class available for use in the United States.¹²⁷ At least 2 orally active selective V_2 -receptor antagonists have been shown to be effective therapy for hyponatremia caused by heart failure, cirrhosis, and SIADH, and manufacturers currently are seeking approval from the Food and Drug Administration.¹²⁸

A potent inhibitor of CYP3A4, conivaptan interacts with many medications including the statins. Concern about serious drug-drug inter-

actions led the United States Food and Drug Administration to limit its approval to the intravenous form of conivaptan to be used for the short-term management of euvolemic hyponatremia and hyponatremia caused by heart failure in hospitalized patients. Conivaptan is contraindicated in hypovolemic hyponatremia (because the antagonism of the V_{1A} receptor could cause hypotension) and in hyponatremia caused by cirrhosis with ascites (because of the theoretical risk of precipitating hepatorenal syndrome, a disorder ameliorated by agonists of the V_{1A} receptor). On the other hand, the hemodynamic effects of V_{1A} receptor antagonists may be favorable in patients with heart failure.¹²⁹

Vasopressin antagonists have been shown to be more effective than placebo in increasing the serum sodium concentration in patients with modest, asymptomatic hyponatremia.^{128,130,131} However, at the doses tested, not all patients responded. Furthermore, there is almost no published experience with the use of these agents in patients with symptomatic hyponatremia. Therefore, vasopressin antagonists cannot

yet be recommended as single agents for the treatment of hyponatremic emergencies. They could be used as dose-sparing adjunctive therapy with hypertonic saline.

Because these agents cause a brisk and relatively prolonged water diuresis in some patients, V_2 -receptor antagonists may risk overly rapid correction and osmotic demyelination if they are used to treat severe chronic hyponatremia. In clinical trials, despite protocols designed to avoid overcorrection, the serum sodium concentration increased by more than 12 mmol/L/d in 4 of 223 hyponatremic patients treated with Tolvaptan,¹³² in 2 of 55 patients treated with Conivaptan,¹³¹ and 3 of 26 patients treated with Sativaptan.¹³⁰ To date, there have been no reported cases of osmotic demyelination caused by a vasopressin antagonist in human beings. However, patients with extremely low serum sodium concentrations, the most likely to experience inadvertent overcorrection (Fig. 1), were excluded from clinical trials of vasopressin antagonists. In an experimental model of chronic hyponatremia, increasing the plasma sodium concentration with a V_2 -receptor antagonist was comparable with hypertonic saline in causing osmotic demyelination.¹³³

Administration of high doses of desmopressin to halt a water diuresis induced by vasopressin antagonists is a theoretically attractive, but as yet untested, strategy that would allow more therapeutic precision than currently is possible. While awaiting more data, clinicians using vasopressin antagonists to treat hyponatremia are advised to monitor urine output closely and be prepared to match it to avoid inadvertent overcorrection.

CONCLUSIONS

Hyponatremia is said to be the most common electrolyte disturbance we treat and the most likely to lead to permanent or lethal complications if it is treated incorrectly. It is unfortunate that we have spent nearly 25 years in therapeutic debates based on embarrassingly limited data. Hopefully, the new availability of vasopressin antagonists will spawn cooperative trials that will generate answers to the many remaining questions about the treatment of this challenging disorder.

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