

Management of Severe Hyponatremia: Rapid or Slow Correction?

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Case reports and the literature on the treatment of severe hyponatremia were reviewed. It appeared that the conflicting opinions with respect to the rate of correction of severe hyponatremia could be reduced to not differentiating between acute and chronic hyponatremia, to using different criteria for this distinction, and to differences in treatment strategy. After reviewing the available data in the literature, it is suggested that hyponatremia should be classified as acute whenever the rate of decrease of serum sodium exceeds 0.5 mmol/L/hour. If it is unknown at which rate the hyponatremia has developed, it can be assumed to be acute if within a short period of time (two to three days), large quantities of fluid are ingested orally or administered parenterally, especially hypotonic fluids in the presence of impaired water excretion. In other cases, chronic hyponatremia is probable. It is concluded that acute hyponatremia should be treated without delay and rapidly at a rate of at least 1 mmol/L/hour, to prevent severe neurologic damage or death. With respect to chronic hyponatremia, it appeared that severe neurologic complications almost exclusively occurred in patients who were treated with hypertonic or isotonic saline without the addition of furosemide or an osmotic diuretic agent, resulting in a (rapid) correction rate of 0.5 mmol/L/hour or more. In contrast, patients with severe chronic hyponatremia treated with furosemide and isotonic or hypertonic saline almost uniformly did well after rapid correction. Uneventful recovery is also the rule when severe chronic hyponatremia is corrected slowly, at a rate less than 0.5 mmol/L/hour. On pathophysiologic grounds, and bearing in mind that slow correction was used in the majority of reported patients in the literature with severe chronic hyponatremia who recovered without neurologic complications, this treatment modality is preferable. Whenever the available data do not permit a differentiation between acute or chronic hyponatremia, rapid correction has to be pursued by means of administration of hypertonic or isotonic saline together with furosemide.

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The treatment of severe hyponatremia is controversial in the recent medical literature [1-8].

It is generally agreed that severe hyponatremia is a disorder with high morbidity and mortality rates. However, the treatment of hyponatremia is also associated with morbidity, especially with brain damage [2,4,6]. The controversy in the medical literature pertains to the rate at which hyponatremia should be corrected.

Advocates of rapid correction argue that if severe hyponatremia remains untreated for a longer period, neurologic damage or death will result, and therefore, a rapid rise of serum sodium concentration should be pursued [1,7]. Moreover, these authors are not convinced that rapid correction as such can be deleterious if this correction is performed appropriately.

On the contrary, rapid correction of severe chronic hyponatremia has been reported to be associated with neurologic complications, particularly central pontine and extrapontine myelinolysis [2,4,6].

Sterns *et al* [2] concluded that uneventful recovery is the rule when severe chronic hyponatremia is corrected slowly at a rate less than 12 mmol/L/day. Additionally, they argued from their own data that uncorrected chronic hyponatremia itself cannot be implicated as the causative agent of neurologic damage [6]. With regard to acute hyponatremia, Sterns *et al* [2] agreed on rapid correction.

We reviewed the literature in order to shed some light on the problem of the correction rate of hyponatremia, especially in regard to the rate of development of the hyponatremia.

PATHOPHYSIOLOGIC CONSIDERATIONS

The extracellular and intracellular fluids are in osmotic equilibrium because water diffuses freely through the cell membranes. A decrease in the serum sodium concentration is expected to cause a shift of water from the extracellular to the intracellular compartment, resulting in generalized cellular edema.

Unlike extracranial tissues, swelling of the brain is limited by the meninges and cranium; this is the most important explanation of the neurologic symptoms of hyponatremia. Cerebral edema and herniation of the brainstem have been found in patients who died of severe acute hyponatremia [1,9-13].

This sequela has not been reported in patients with chronic hyponatremia. However, the rate of decrease of serum sodium or the magnitude of the hyponatremia that differentiates between patients with acute and chronic hyponatremia is not known.

Induction of acute hyponatremia (serum sodium lowered to 119 mmol/L in two hours) in experimental animals was followed by high mortality (88%) with gross evidence of brain edema. The brain content of sodium, potassium, and chloride (mmol/kg dry weight) was normal [14].

TABLE I

Rate of Development of Hyponatremia and the Correction Rate in 38 Patients with Severe Hyponatremia of 120 mmol/L or Below Reported in the Literature*

Rate of Decrease (mmol/L/hour)	Correction Rate (mmol/L/hour)			Total Number
	<1	1 to 2	≥2	
<0.5	5 (-,-)†	—	2 (-,-)	7 (-,-)
0.5 to 1	9 (-,1)	6 (-,1)	5 (-,-)	20 (-,2)
1 to 2	3 (3,-)	1 (-,1)	1 (1,-)	5 (4,1)
≥2	—	2 (-,-)	4 (-,1)	6 (-,1)
Total number of patients	17 (3,1)	9 (-,2)	12 (1,1)	38 (4,4)

* Case reports from [10–13,16–32].

† The first number in parentheses refers to the number of deaths; the second number refers to the number of patients with persistent neurologic sequelae.

In experiments with a more gradually (chronic) induced hypotonicity, it appeared that brain cells, unlike other tissues, can prevent massive swelling by extruding electrolytes [14,15]. These experiments also seemed to indicate that the rate of adaptation varied between species and individuals. These experimental data suggest that brain edema is the consequence when a plasma-to-brain osmotic gradient reaches a critical level before the adaptation process of extruding intracellular electrolytes has fully developed. Rapid correction of serum sodium concentration, under such circumstances, probably will prevent the plasma-to-brain osmotic gradient from becoming critical, and thus prevents cerebral edema. Whenever adaptation of the brain cells occurs and a new osmotic equilibrium has been established, a rapid rise in serum sodium concentration will induce a shift of water from the intracellular to the extracellular compartment. There is good clinical and experimental evidence that this can also cause brain damage.

In order to study the effect of treatment on outcome of severe hyponatremia, we believe it is essential to differentiate between patients who develop hyponatremia rapidly (acute), before the adaptive mechanism of extruding electrolytes by the brain has occurred, and patients who have a more gradual (chronic) decline of their serum sodium concentration, when the brain has adapted to the hypotonic environment before treatment is started.

EVALUATION OF CASE REPORTS SELECTED FROM THE LITERATURE

We reviewed the reports from patients with a serum sodium concentration below 121 mmol/L in which enough data were provided to analyze the rate of development of hyponatremia, the rate of correction, treatment strategy, and outcome. In this respect, we discuss the observations published on a total of 163 patients. Additionally, we review two reports by Arieff [1] and Arieff and Fraser [9] that provide information on rapidly developing hyponatremia. Because no individual data are provided in these two reports, these patients are not included in our analysis of case reports.

In 38 of the reported cases, both the rate of development and the correction rate could be derived from the available data. Hyponatremia was due to oxytocin in-

fusion combined with large amounts of hypotonic fluids (11 patients), postoperative administration of large amounts of hypotonic fluids (13 patients), polydipsia (six patients), and miscellaneous causes (eight patients). Four of these 38 patients died, and gross or microscopic cerebral edema was found at autopsy [10–13]. In all four patients, treatment of the hyponatremia was started after the patients had experienced a respiratory arrest necessitating artificial ventilation. Persistent neurologic sequelae occurred in four other patients [16–18]. One of the four patients with neurologic complications had also experienced a respiratory arrest followed by artificial ventilation before treatment of hyponatremia was started. The other three patients were treated with a delay ranging from three to 24 hours.

The mean serum sodium concentration at diagnosis did not differ markedly between the 30 patients who recovered (103.2 mmol/L [range: 98 to 118 mmol/L]), the four patients with neurologic complications (105.2 mmol/L [range: 95 to 111 mmol/L]), and the four patients who died (110.5 mmol/L [range: 104 to 116 mmol/L]). From Table I, it can be inferred that morbidity and mortality only occurred in these 38 cases when the rate of development of hyponatremia was 0.5 mmol/L/hour or more. With regard to the association between the rate of correction and outcome, the data in Table I are inconclusive because irreversible neurologic damage apparently occurred before treatment was initiated. It can only be stated that rapid correction in these cases is not harmful.

Arieff [1] described 15 previously healthy normonatremic women with severe postoperative hyponatremia (on average 108 mmol/L at diagnosis, about 49 hours after surgery). Four patients died, three with evidence of brain edema at autopsy. Among the 11 surviving patients, nine remained in a permanent vegetative state. Two patients regained consciousness but were left with permanent neurologic disability. Hyponatremia developed in 28 ± 4 hours in the four patients who died, which was much faster compared with the time in the other 11 patients who developed hyponatremia (57 ± 8 hours). Although no individual data are provided, the rate of decrease of serum sodium can be estimated at about 1 mmol/L/hour in the four patients who died and at about 0.5 mmol/L/hour in the other 11 patients. Patients were treated after an average delay of 16 ± 7 hours with various concentrations of sodium chloride often combined with furosemide. The correction rate was on average 0.5 mmol/L/hour. It is striking that in the two patients who regained consciousness, therapy was started within one hour and that their serum sodium concentration increased most rapidly (1 mmol/L/hour).

Arieff and Fraser [9] described another seven previously healthy female patients with a decline in serum sodium concentrations from 139 ± 1 mmol/L to 116 ± 3 mmol/L over a mean of 37 hours (average rate of decrease 0.6 mmol/L/hour). Hyponatremia was the result of the administration of a 5% glucose solution after surgery in six patients and self-induced water intoxication in one patient. All patients died without treatment and all showed cerebral edema at autopsy.

The data from these two reports were also reviewed in order to determine which rate of decrease of serum sodium should be considered either acute or chronic. Overall, these data indicate that a rate of about 0.5

mmol/L/hour marks the boundary line between acute and chronic hyponatremia.

In the majority of patients with hyponatremia reported in the literature, no data were available to assess the rate of decrease of serum sodium, but the history and the clinical data can generally offer enough information to differentiate chronic from acute hyponatremia. It is reasonable to assume that a rapid (acute) decline in serum sodium concentration (more than 0.5 mmol/L/hour) can only develop after the intake of large quantities of fluid, either orally or by parenteral administration of hypotonic fluids, in particular in patients with impaired water excretion. Whenever the history and clinical data rule out acute hyponatremia on the basis of the aforementioned assumptions, hyponatremia probably has developed gradually and can be assumed to be chronic.

With these assumptions in mind, we found eight patients [20,33-35], in addition to the 31 patients described in Table I, who developed acute hyponatremia. The information gained from these additional cases did not permit another conclusion than the one already drawn from Table I.

Thus, considering the available data concerning patients with proven or probable acute hyponatremia, it appears that immediate treatment is mandatory. Without treatment, death or severe neurologic sequelae are to be expected. Treatment should certainly include the removal of causative factors if possible. The data reported by Arieff [1] suggest that rapid correction can be beneficial. In support of rapid correction of acute hyponatremia are data provided by Sterns [6], who corrected hyponatremia rapidly in patients with assumed acute hyponatremia. No individual data were provided. The initial serum sodium concentration averaged 105 mmol/L, and the correction rate was 1.57 mmol/L/hour. None of 10 patients experienced neurologic sequelae. We found no reports that substantiated that rapid correction of acute hyponatremia can be detrimental.

We were able to find 117 patients in the literature with assumed chronic hyponatremia (rate of development less than 0.5 mmol/L/hour) and for whom enough data were provided to analyze the influence of correction rate on outcome. Thiazide diuretic agents and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) appeared to be the prominent causes of severe chronic hyponatremia (Table II). The most frequent reported neurologic complication related to correction of severe chronic hyponatremia was central pontine myelinolysis (CPM). Clinically, this syndrome appears as a rapidly evolving paraparesis or quadriparesis, dysarthria, dysphagia, and, commonly, systemic hypotension [4,63,78]. Besides rapid correction of chronic hyponatremia, other electrolyte disorders, alcoholism, malnutrition, toxins, and metabolic imbalance have been proposed as causative factors in the development of CPM [4,63]. As originally described, the name of the syndrome accurately reflects the pathologic findings. However, more recently, patients have been described with demyelinating lesions outside the pons found at autopsy after correction of hyponatremia [2,43,52,55,77]. Persistent coma or paraparesis was reported in some other patients after treatment of hyponatremia. The available information did not permit the diagnosis of CPM.

In 71 of the 117 patients, hyponatremia was correct-

TABLE II

Cause and Serum Sodium Concentration at Diagnosis in 117 Patients with Severe Chronic Hyponatremia Described in the Literature*

Cause	Serum Sodium (mmol/L)				Total Number
	<105	105 to 110	110 to 115	115 to 120	
Diuretics	24	18	11	5	58
SIADH	10	9	7	12	38
Volume depletion	3	—	—	2	5
Miscellaneous or unknown†	9	2	3	2	16
Total number	46	29	21	21	117

* Case reports from [2,4,6,20,25,36-77].

† Stress, Addison's syndrome, potomania.

TABLE III

Initial Sodium Level, Rate of Correction, and Neurologic Sequelae in 117 Patients with Severe Chronic Hyponatremia Reported in the Literature

Initial Serum Sodium (mmol/L)	Correction Rate (mmol/L/hour)		
	<0.5	0.5 to 1.0	≥1
<105			
Total number	10	20	16
CPM	—	9	10
Other neurologic sequelae	—	7	3
105 to 110			
Total number	12	8	9
CPM	—	3	1
Other neurologic sequelae	—	1	1
110 to 115			
Total number	9	10	2
CPM	—	5	2
Other neurologic sequelae	—	1	—
115 to 120			
Total	15	3	3
CPM	1	—	—
Other neurologic sequelae	—	—	—
Total number	46	41	30
CPM	1	17	13
Other neurologic sequelae	—	9	4

CPM = central pontine myelinolysis.

ed at a rate of 0.5 mmol/L/hour or more. One of the aforementioned neurologic sequelae developed in 43 (62.3%) of these 71 patients (Table III). In contrast, only one of 46 patients developed CPM after correction of hyponatremia at a rate below 0.5 mmol/L/hour (p <0.005). Moreover, in the particular case reported by Norenberg *et al* [4] (Case 12), it is doubtful whether the CPM should be ascribed to the correction of the hyponatremia rather than to the preexisting chronic alcoholism and hepatic failure. In most patients, neurologic sequelae developed after an initial improvement of the neurologic condition following correction of hyponatremia.

Ayus *et al* [7] suggested that factors other than rapid correction of hyponatremia may cause neurologic complications. In the 71 patients with chronic hyponatremia that was corrected at a rate of 0.5 mmol/L/hour or more, we evaluated, to the extent that data allowed us, the role of different treatment modalities, alcohol-

TABLE IV

Severe Chronic Hyponatremia Corrected at 0.5 mmol/L/hour or More: Treatment Modality and Neurologic Sequelae

Treatment Modality	Neurologic Sequelae		Total Number
	Absent	Present	
Saline only*	7	34	41
Saline plus furosemide†	13	2	15
Urea, sodium supplementation, water restriction‡	4	—	4

* Case reports from [2,4,6,36-38,40,43,45,47,48,52,55,57,61,63,64,67,70,71,73,77].

† Case reports from [4,39,42,75].

‡ Case reports from [49].

ism, and overcorrection to hypernatremic levels. In 41 cases, hypertonic or isotonic saline was administered without a diuretic agent. Neurologic sequelae developed in 34 patients (Table IV). In contrast, only two of 15 patients treated with saline (most hypertonic) and furosemide had an unfavorable outcome ($p < 0.005$). The two patients, both of whom were described by Norenberg *et al* [4], had serious underlying diseases and their hyponatremia was overcorrected to hypernatremic levels. Severe hyponatremia in the other 13 patients [39,42,75] treated with (hypertonic) saline and furosemide was caused by SIADH or by the administration of diuretics. Decaux *et al* [49] rapidly corrected hyponatremia in four patients caused by SIADH with urea, water restriction, and oral sodium supplementation. All four patients experienced a complete recovery. These results suggest that administration of furosemide prevents neurologic damage after rapid correction of severe chronic hyponatremia with (hypertonic) saline. Probably the same holds for treatment with urea, water restriction, and sodium supplementation. With both treatment strategies, a negative water balance is created rather than a positive sodium balance, resulting in a (rapid) increase in the serum sodium concentration.

Ayus *et al* [7] suggested, partially based on experimental data [79], that a rapid conversion of hyponatremia to normonatremia or hypernatremia, or an increase in the serum sodium concentration of more than 25 mmol/L in the initial 48 hours of therapy, or both, produces the demyelinating lesions of the brain rather than a high correction rate in itself. Their suggestion is not supported by their own clinical data, as already pointed out by Ellis *et al* [8] (see also [78]).

We could find 12 patients [2,6,37,47,57,61,71] out of the 43 with severe neurologic sequelae after a rapid initial correction of hyponatremia, with a total serum sodium rise in the first 48 hours less than 25 mmol/L. Additionally, eight of these 12 patients developed neurologic complications before complete correction of hyponatremia. If correction to normonatremia in itself could be detrimental as contended by Ayus *et al* [7], one would expect a high incidence of neurologic sequelae after rapid correction of less severe hyponatremia (initial levels: 115 to 120 mmol/L). This cannot be concluded from the data in Table III.

Hypernatremia developed in seven of 43 patients [2,4,67] with neurologic sequelae and a correction rate of 0.5 mmol/L/hour or more. However, in some of these patients, neurologic deterioration occurred be-

fore hypernatremic levels were reached. These results are insufficient to support the hypothesis that overcorrection of hyponatremia to hypernatremia is followed by brain damage.

Alcohol abuse was reported in 12 of 43 patients with neurologic sequelae following rapid correction of chronic hyponatremia. We found only one patient with severe chronic hyponatremia and alcohol abuse who did not develop neurologic complications after rapid correction. These results suggest that alcoholism predisposes to neurologic injury after rapid correction of severe chronic hyponatremia. In contrast, Sterns [6] could not find an association between alcoholism and posttreatment neurologic complications in a retrospective analysis of 64 episodes of severe hyponatremia in 62 patients. With the data that are currently available, the precise role of alcoholism cannot be elucidated. In the majority of patients described in the literature, the rate of correction is the only factor that can be connected with the neurologic sequelae.

From this review, it can be concluded that slow correction, less than 0.5 mmol/L/hour, of severe chronic hyponatremia results in uneventful recovery, whereas rapid correction, 0.5 mmol/L/hour or more, is associated with a high rate of neurologic complications, in particular when patients are only treated with (hypertonic) saline. These results correspond to the findings of Sterns *et al* [2], who reviewed published reports on patients with very severe hyponatremia (serum sodium less than 106 mmol/L/hour). The data we gathered suggest that furosemide, and probably osmotic diuretic agents like urea, can prevent neurologic morbidity whenever hyponatremia is corrected at a high rate by administration of isotonic or hypertonic saline.

COMMENTS

In the medical literature, no consensus exists as to the optimal rate of correction of severe hyponatremia. Some authors recommend rapid correction, whereas others believe that a more cautious approach is warranted. In reviewing the literature on this subject, we noted that the advocates of rapid correction did not differentiate, or did so based on disputable criteria, between acute and chronic hyponatremia [7,20]. On pathophysiological grounds, such a division of patients seems worthwhile.

Much of the disagreement between authors probably would not exist if all authors had differentiated between acute and chronic hyponatremia, or agreed on the criteria for such a distinction. On the basis of the data available in the literature, we suggest that hyponatremia should be classified as acute whenever the rate of decrease of serum sodium exceeds 0.5 mmol/L/hour. In cases in which the precise onset and duration of hyponatremia are unknown, it can be assumed to be acute if within a short period of time (two to three days), large quantities of fluids are ingested orally or administered parenterally, especially hypotonic fluids in the presence of impaired water excretion. In other cases, chronic hyponatremia is likely.

With respect to acute hyponatremia, the available data from the literature indicate that immediate correction and possibly also rapid correction, at least 1 mmol/L/hour, can prevent severe morbidity or mortality. Discordant results have been described regarding rapid correction of severe chronic hyponatremia. In agreement with the results of Sterns and associates

[2,6], we found that neurologic sequelae developed almost exclusively in patients whose hyponatremia was corrected at a rate equal or above 0.5 mmol/L/hour. Patients whose hyponatremia was corrected at a lower rate had an uneventful recovery except for a few patients with severe underlying conditions. In searching for factors other than rapid correction that could be responsible for neurologic complications, we found that patients whose hyponatremia was rapidly corrected with only isotonic or hypertonic saline were susceptible to complications, in contrast to patients treated with furosemide and isotonic or hypertonic saline who almost uniformly did well after rapid correction. Much of the disagreement between authors on this subject can be traced back to this apparently very important difference in treatment strategy.

In view of the pathophysiology and the fact that the majority of reported cases in the literature with severe chronic hyponatremia, who recovered without neurologic sequelae, were corrected slowly, we recommend slow correction, at a rate less than 0.5 mmol/L/hour, of established chronic hyponatremia.

If doubt exists about the rate at which hyponatremia has developed, and the clinical data permit no differentiation between chronic and acute hyponatremia, rapid correction to mildly hyponatraemic levels with hypertonic saline and furosemide is probably the best strategy. Acute hyponatremia should be corrected immediately and rapidly to mildly hyponatraemic levels, at a rate in excess of 1 mmol/L/hour.

More definitive treatment regimens have to be derived from carefully designed prospective studies rather than literature reviews.

Ayus *et al* [7] were the first to report the results of a prospective study but, as extensively discussed [8], with too many shortcomings to permit firm conclusions with regard to the optimal therapeutic approach of severe hyponatremia.

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