Kidney International, Vol. 42 (1992), pp. 1662–1667

Treatment of chronic hyponatremia in rats by intravenous saline: Comparison of rate versus magnitude of correction

ALAIN SOUPART, RAYMOND PENNINCKX, ALAIN STENUIT, OLIVIER PERIER, and GUY DECAUX

Research Unit for the Study of Hydromineral Metabolism, Department of Internal Medicine and Laboratory of Chemical Biology, Erasmus University Hospital, and Department of Neuroanatomy, School of Medicine, Free University of Brussels, Brussels, Belgium

Treatment of chronic hyponatremia in rats by intravenous saline: Comparison of rate versus magnitude of correction. The role of the rate of correction in the development of demyelinating brain lesions after correction of chronic severe hyponatremia is controversial. It has been recently suggested in rats treated by intravenous (i.v.) hypertonic saline (NaCl) that both the rate and the absolute change in serum sodium represent critical risk factors. However, we previously demonstrated in rats treated by intraperitoneal (i.p.) injections of NaCl that below a threshold of serum sodium rise of 20 mEq/liter/24 hr, only 5% of the brain lesions were recorded, even in rats submitted to a rapid (1 hr) serum sodium increment following the i.p. injection. Working below this threshold (serum sodium rise < 20 mEq/liter/24 hr) in the present work, allowed us to independently determine the role of the rate in the outcome of the correction. This was done by submitting the rats to a rapid (1 hr) intravenous infusion of NaCl. As a difference between the i.p. and i.v. route in the degree of volume expansion produced by the NaCl administration could also play a role in the pathogenesis of the brain lesions, rats treated with rapid i.v. infusion of NaCl (associated with volume expansion) were compared to a group of rats treated with water restriction (associated to volume contraction) to evaluate the role of volemia on the incidence of neurological damage. Hyponatremia was induced over three days with d-glucose in water and vasopressin. The group 1 was corrected by intravenous (i.v.) infusion of hypertonic saline over one hour. Rats achieved a serum sodium correction of 12 ± 0.5 mEq/liter (8 to 17 mEq/liter) at the end of the infusion and of 13.5 ± 0.6 mEq/liter (8 to 19 mEq/liter) after the first 24 hours. Group 2 was submitted to spontaneous correction with water restriction over 48 hours. The maximum daily increment in serum sodium observed during this period in this group was 14.8 ± 0.5 mEq/liter (9 to 19 mEq/liter). No difference could be observed in the incidence of brain lesions between both groups. Only one rat (1 of 25) was damaged in group 1 and two rats (2 of 24) in group 2, an incidence similar to our previous results. We conclude that: (1) A rapid (1 hr) and large (12 mEq/liter, range 8 to 17 mEq/liter in 1 hr) rise in serum sodium after NaCl administration is well tolerated provided that the limit of daily absolute change in serum sodium (20 mEq/liter/24 hr) is not exceeded. In these conditions, the rate of the correction is not important; (2) In the same conditions, a correction associated with an acute (1 hr) volume expansion (NaCl i.v.) is not more toxic for the brain than water restriction (volume contraction) alone.

The mechanisms responsible for the development of the brain demyelinating lesions which can develop after the correction of severe (<115 mEq/liter) chronic (>48 hr) hyponatremia remain highly controversial [1–5]. Brain demyelinating lesions are probably the result of the osmotic stress induced by the serum sodium rise which can lead to excessive brain dehydration [6]. Supporting this hypothesis, recent experiments suggest that the initial damage could be a mechanical separation of the axon from its surrounding myelin sheath, as observed shortly after an "excessive" osmotic gradient [7, 8]. Factors like hypokalemia [9], nutritional status or hypoxic insult [10] could also contribute to the pathogenesis of brain damage, independently of the correction methods. However, disagreement particularly concerns the respective role of the magnitude and of the rate of serum sodium correction in the pathogenesis of brain demyelination [1, 11, 12]. Yet, recent animal experiments have provided important data by demonstrating the critical role played by the absolute change in serum sodium in the development of brain damage [13–15]. Likewise, we recently reported in rats corrected over 48 hours that the first brain lesions appear, for 95% of the injured rats, when the daily absolute change in serum sodium reached 20 mEq/liter/24 hr. Below this limit, the incidence and severity of brain lesions were very low, even in the group corrected with intraperitoneal (i.p.) bolus injections of hypertonic saline (NaCl) and despite the fact that this method leads to a rapid (1 hr) and large (mean value 19 mEq/liter) increment in serum sodium [15]. We concluded from these observations that the critical factor for the brain is the threshold of absolute change in serum sodium as proposed in previous studies [12–14] (this limit is, however, not entirely independent of the concept of rate of correction as it is defined for a 24 hr period of time). Our results also suggested that below this limit of 20 mEq/liter/24 hr the rate of correction is probably not important. On the contrary, Verbalis, Martinez and Dutarosky recently showed in data pooled from chronic hyponatremic rats corrected by either slow intravenous (i.v.) infusion of NaCl or water restriction, that the incidence of brain lesions was 64% when the maximal correction rate exceeded 4 mEq/liter/hr at a given time or if the daily rise in serum sodium exceeded 25 mEq/liter/24 hr. They concluded that brain damage is a function of both rate and magnitude of correction [16]. In an attempt to elucidate this apparent discrepancy about the exact role of the correction rate, two different approaches were considered.

Firstly, the previous determination of the toxic threshold for the brain of daily serum sodium increment permits, by working below this limit, evaluation of the rate of correction as an

Received for publication October 29, 1991
and in revised form January 15, 1992
Accepted for publication January 16, 1992

independent risk factor in the development of demyelinating lesions.

The second issue concerns the susceptibility of the brain to the degree of volume expansion induced by the correction method [16]. Intraperitoneal injection of NaCl is the method currently used to correct hyponatremia in rats [6, 13–15, 17–19].

However, the i.p. injections are followed, during the early hours, by a shift of water into the peritoneal cavity and a fall in arterial pressure [18, 19], so that the degree of volume expansion could be initially less important in the i.p. model than with the intravenous NaCl route.

If there is no doubt that fluid restriction (volume contraction) alone can produce demyelination [12, 13, 20], it is conceivable that an acute volume expansion produces a more deleterious effect on the brain, explaining a higher susceptibility to the correction rate in rats treated with the i.v. model of NaCl administration [16].

Methods

Animals

The study was performed on male Wistar rats ($N = 59$) weighing 400 to 550 g (aged 3 to 5 months).

Animals were housed in individual cages and were allowed 10 days to adapt before starting the study, with free access to pelleted rat chow and tap water. Room temperature was controlled (20°C) with lights on from 7 a.m. to 7 p.m.

Induction of severe chronic hyponatremia (days 1 to 3)

Profound (<115 mEq/liter) chronic hyponatremia was induced as previously described [13, 14]. Rats received subcutaneous injections of 0.5 U of vasopressin tannate in oil (Parke-Davis) per 100 g body wt and intraperitoneal injections of 2.5% (140 mM) d-glucose in water equivalent to 5% initial body wt twice daily (09 a.m. and 17 p.m.) on day 1, to 3% initial body wt once daily (12 hours) on day 2, and 3% initial body wt twice daily on day 3. Animals were kept under light ethyl ether anesthesia at time of injection. Animals had no access to food or water during this phase of the experiment [15].

Correction of hyponatremia (days 4 and 5)

Two separated groups of rats were studied. The correction was performed in a 48 hour period of time, consisting of the administration of intravenous NaCl over one hour and then water restriction in one group, and of water restriction alone in the other. In our previous work [15] where the rats were corrected over 48 hours, we observed that the animals achieved, without predictive clues, a large increment in serum sodium ($M\Delta S_{Na}$) one of the two days, and a lower rise in serum sodium the other day. However, no difference could be observed in the incidence or severity of brain lesions whether the large increase in serum sodium occurred during the first or the second correction day. In both groups, rats had free access to the laboratory diet and tap water from day 6 to day 8 (time of death) [15].

Group 1 ($N = 25$)

In this group, rats had indwelling femoral venous polyethylene catheters (PE-10, Clay-Adams, Becton Dickinson, Parsippany, New Jersey, USA) inserted on day 4, just before the NaCl administration under pentobarbital sodium anesthesia (Nembutal, Abbott, 25 mg/kg i.p.). This enabled continuous rapid infusion of hypertonic saline at a controlled rate via syringe pumps (model 11, Harvard Apparatus, South Natick, Massachusetts, USA). Hypertonic saline (1 M NaCl) was infused at a rate of 1 ml/100 g body wt/hr during one hour to produce a rapid and significant increment in serum sodium concentration, but which did not exceed the threshold of 20 mEq/liter.

After 60 minutes, the infusion was stopped and the femoral catheter was removed. Rats were then maintained in their cages from day 4 to day 8 with no access to food and water during the two days of the correction period (day 4 and 5). Subcutaneous injections of vasopressin were continued (0.5 U/100 g once a day) from day 4 to day 8 to avoid excessive correction (change in serum sodium maintained <20 mEq/liter/day) during this period. Blood samples (0.25 ml) were collected via tail transection while the rats were under light ether anesthesia. Blood was drawn: on day 4 to measure serum sodium at time of hyponatremia, just before the NaCl infusion; at the end (1 hr) of the perfusion and on day 5 (24 hr after treatment); day 6 (48 hr after treatment); day 7 (72 hr after treatment); and on day 8 (at time of death). Serum sodium was measured after centrifugation (3000 × g for 10 min) via ion-specific electrodes (Microlyte, Kone, Espoo, Finland).

In 10 out of the 25 rats, plasma proteins (10 μl) (quantitative colorimetric determination, Vitalab 21, Vital Scientific Industries, Dieren, The Netherlands) and microhematocrit were measured on day 4, just before correction and at the end (1 hr) of the i.v. NaCl administration. Microhematocrit was measured in duplicate in each sample collected at the same time as protein measurements were done. Ten additional animals not included in the initial group of 25 rats were used as controls in normal conditions for serum sodium, plasma proteins concentration and microhematocrit determinations.

Group 2 ($N = 24$)

In this group, rats were submitted to spontaneous correction under water restriction, with no access to water and food during the correction period (days 4 and 5). Injections of vasopressin were stopped on day 4. Serum sodium was measured every 24 hours from day 4 to day 8 (at time of the death).

Histological examination of the brains

During day 4 to day 8, rats were weighed daily and closely observed and any neurological dysfunction was recorded. On day 8, rats were decapitated and the brain removed and immediately placed in 10% buffered formaldehyde for ten days. Afterwards, brains were sectioned coronally at six levels, and processed for light microscopy as previously described [15, 21]. Briefly, sections were stained with hematoxylin-eosin for evaluation of neuronal density and Luxol fast blue for evaluation of myelin integrity. The sections were independently examined by two neuropathologists (O.P.; A.ST.) without knowledge of the treatment group of the animals.

Statistical analysis

All values are expressed as means ± SE. To determine statistical difference of various parameters between different

Table 1. Comparison of S_{Na}, ΔS_{Na} values and brain lesions between rats treated with rapid (1 hr) intravenous infusion of hypertonic saline and rats corrected by water restriction

	S_{Na} at time of hyponatremia (day 4)	ΔS_{Na} at the end of NaCl i.v. infusion (1 hr)	ΔS_{Na} 24 hr after NaCl i.v. infusion (day 5)	$M\Delta S_{Na}$	S_{Na} at time of death (day 8)	No. of rats with brain lesions	Location of brain lesions
Group 1 (N = 25)	102 ± 1.2	12 ± 0.5	13.5 ± 0.6	—	137 ± 0.8	1/25	Thalamus symmetrical
Range	(90–113)	(8–17)	(8–19)		(126–144)		(N = 1)
NaCl i.v.							
Group 2 (N = 24)	104 ± 1.1	—	—	14.8 ± 0.5	137 ± 0.5	2/24	Thalamus symmetrical
Range	(91–114)			(9–19)	(130–143)		(N = 2)
Water restriction							

Data are means ± SE. Abbreviations are: S_{Na}, serum sodium; ΔS_{Na}, absolute change in S_{Na}; $M\Delta S_{Na}$, maximum daily ΔS_{Na} observed in group 2 during one of the two days of the correction period (day 4 or 5).

The other days, the mean ΔS_{Na} are 3.4 ± 0.6 mEq/liter (day 5) and 12 ± 0.9 mEq/liter (day 6) for group 1, and 9 ± 0.6 mEq/liter (day 4 or 5) and 5 ± 1 mEq/liter (day 6) for group 2.

groups, conventional t-tests and paired t-test for difference within groups at different times were used.

Results

In the present study, including a total of 59 rats, the serum sodium values at time of hyponatremia (day 4) were similar in both group 1 and 2 (Table 1) and all rats presented severe (<115 mEq/liter) hyponatremia. We have observed a mortality rate of 10% during the induction of hyponatremia which is lower than in our previous experiments [15, 21].

This can be explained by the lower total amount of fluid infused in the present model. It must be noted that in the different animal studies, the mortality rate ranged from 63% to 20% [14, 22, 23].

For each rat in both groups, the daily change in serum sodium never exceeded 19 mEq/liter/24 hr from day 4 to day 8.

Group 1: Rapid correction with intravenous NaCl

The purpose of this protocol was to evaluate the tolerance of a rapid (1 hr) correction of the serum sodium but with an absolute change remaining below the threshold of 20 mEq/liter/24 hr. This has been achieved in 25 rats with a method of correction (intravenous NaCl) which produces a concomitant volume expansion.

At the time of hyponatremia, the rats stayed motionless and drowsy in their cages with relatively few responses to stimulation. No convulsions or respiratory arrests were recorded. The one hour infusion of NaCl produced a mean increment in serum sodium of 12 ± 0.5 mEq/liter (range 8 to 17 mEq/liter), (+11%) which increased the serum sodium to a mean level of 114 ± 1.1 mEq/liter (range 107 to 125). Immediately after awaking from their anesthesia, the rats became alert with normal neurological function. Natremia did not increase significantly during the subsequent hours and the mean change in the first 24 hours (day 4) was 13.5 ± 0.6 mEq/liter (range 8 to 19 mEq/liter). As for the first day of correction, all the rats achieved during the subsequent days a daily rise in serum sodium below the limit of 20 mEq/liter/24 hr with mean daily increment of 3.4 ± 1.0 mEq/liter during the second day (day 5, range 0 to 12) and 12 ± 0.9 mEq/liter (range 1 to 18) on day 6. The larger increment on day 6 is explained by the osmotic diuresis arising when the animals again have free access to food and water [16]. At day 8, all the rats had survived and had corrected their natremia (>135 mEq/liter), except one rat (final natremia 126 mEq/liter).

As shown in Table 1, the maximum daily absolute change in serum sodium during the correction period was similar in group 1 (13.5 ± 0.6 mEq/liter in the first 24 hr) and in group 2 ($M\Delta S_{Na}$, 14.8 ± 0.5 mEq/liter, mean value of the highest increment in serum sodium achieved by the rats during either day 4 or 5).

Brain histology was normal in 24 out of the 25 rats included in this group. None of the 24 undamaged rats presented symptoms. Only one rat developed brain lesions (1 of 25; 4%). This rat was free of symptoms and presented limited (focal) symmetrical demyelinative lesions in the thalamus. Histopathological analysis demonstrated cellular necrosis with gliovascular proliferation, fat loaded cells and demyelination. Its change in serum sodium was 13 mEq/liter after the first 24 hours, 4 mEq/liter on day 5 and 18 mEq/liter on day 6.

The acute volume expansion induced by the intravenous infusion of hypertonic saline is illustrated in ten rats by the changes at the end of the NaCl administration, of the microhematocrit (mean value in hyponatremia 51 ± 2%, after 1 hr NaCl: 45 ± 1; −11%, $P < 0.001$) and the plasma protein concentrations (mean value in hyponatremia 5.6 ± 0.5 g/dl, after 1 hr NaCl: 4.6 ± 0.2; −17%; $P < 0.001$) for a mean increment in serum sodium of 12 ± 0.7 mEq/liter (+11%; mean value in hyponatremia 103 ± 2 mEq/liter; after 1 hr NaCl 115 ± 1.6 mEq/liter; $P < 0.001$).

Control values for serum sodium, hematocrit and plasma proteins were respectively: 139 ± 0.4 mEq/liter, 48 ± 1% and 6.8 ± 0.2 g/dl.

Group 2: Water restriction

The purpose of this protocol was to evaluate the tolerance of a correction by a method producing a volume contraction (water restriction) and to compare it to the group 1 submitted to an acute volume expansion. During the two days of the correction period (days 4 and 5) nine rats achieved their largest absolute change ($M\Delta S_{Na}$) in the first day (day 4, mean value 16 ± 0.6 mEq/liter) and 15 rats in the second day (day 5 mean value 14 ± 0.7 mEq/liter). When the $M\Delta S_{Na}$ of each rat achieved during day 4 or day 5 are pooled, the mean value of $M\Delta S_{Na}$ is 14.8 ± 0.5 mEq/liter (range 9 to 19). This is not different from the mean largest daily increment in serum sodium observed in

group 1 (13.5 ± 0.6 mEq/liter Table 1). Brain analysis was normal in 22 out of the 24 rats included in their group and all of them were free of neurological symptoms. Two rats had brain injuries (2 of 24, 8%). The first one achieved a $M\Delta S_{Na}$ of 14 mEq/liter (achieved on day 5) and was free of symptoms. Diffuse demyelinative lesions were observed symmetrically in the thalamus.

The other rat was symptomatic with paralysis of the limbs. Its $M\Delta S_{Na}$ was 16 mEq/liter (achieved on day 4) and also presented diffuse symmetrical demyelinative lesions in the thalamus. In both rats, the lesions were characterized by gliovascular proliferation, fat loaded cells, cellular necrosis and demyelination.

As shown in Table 1, no difference could be observed in the incidence of brain lesions between rats rapidly corrected via a volume expansion model (1 of 25, 4%) and rats corrected by the volume contraction model (2 of 24, 8%). Provided that the threshold of daily change in serum sodium of 20 mEq/liter defined previously [15] was not exceeded, neither the methods tested here nor the rate of correction were determinant risk factors for subsequent development of brain damage.

Discussion

This work addresses two major questions in view of the optimal management of severe chronic hyponatremia. The first and widely debated one, concerns the rate of correction: is the rapidity of the serum sodium increment a critical factor which must be closely monitored during the therapy of hyponatremia? It is generally accepted that high rates of increase in serum sodium are well tolerated in acute hyponatremia [12, 23, 24] with, however, occasional reports of myelinolysis [19, 25, 26].

Demyelination is more likely to develop after chronic (>48 hr) hyponatremia which renders the brain more susceptible to excessive dehydration during correction [6]. The previous animal experiments, with the exception of the recent work of Verbalis et al [16], did not provide appropriate data allowing us to evaluate the exact role of the correction rate in the development of brain damage. Indeed, studies demonstrating demyelination are characterized by both high rates and large magnitude of serum sodium increment [13, 14, 17].

The present study confirms [11, 14, 15] the hypothesis first advanced by Ayus et al [11], suggesting the lack of influence of the rate on the outcome of the correction, the determinant risk factor being the absolute change in serum sodium during the first 24 hours. Indeed, by using daily changes in serum sodium ranging below the critical threshold to correct chronic hyponatremic rats, this model permitted independent evaluation of the effect of rapid (1 hr) and large (8 to 17 mEq/liter in 1 hr) increments in serum sodium obtained by i.v. infusion of NaCl. At the end of the infusion time, the neurological status frankly improved and symptoms related to hyponatremia disappeared. Despite this overaggressive approach, only one rat (1 of 25, 4%) developed mild demyelinative lesions, an incidence comparable with our previous results in rats corrected either slowly (NaCl i.p. in divided doses, urea) or rapidly (NaCl ± i.p. in boluses) [15]. Although our results demonstrate that for a magnitude of correction remaining <20 mEq/liter/24 hr the rate to achieve this goal does not influence the outcome, these findings do not conflict with the conclusions of Verbalis et al [16]. In their study, demyelinative changes were observed in the brain of 64% of rats whose maximum rate of serum sodium rise exceeded 4 mEq/liter/hr at a given time, or whose total increment in serum sodium exceeded 25 mEq/liter during the first 24 hours. Thus, our rats safely achieved correction rates (12 mEq/liter in 1 hr, range 8 to 17 mEq/liter) largely above the "toxic" limits defined by Verbalis et al. This apparent discrepancy is explained by the fact that their series included few rats submitted to a daily change in serum sodium <20 mEq/liter with concomittant high maximal correction rates (>4 mEq/liter/hr); only three rats presented with these characteristics (maximal correction rates of 5.5, 5.8 and 7 mEq/liter/hr), two of them being injured [16]. Their conclusions are drawn from data obtained in the rats submitted to daily change in serum sodium >20 mEq/liter/24 hr, and over this threshold, the rate of correction probably represents a significant risk factor.

We clearly demonstrated here for the first time that a rapid and large intravenous infusion of hypertonic saline is safe provided that the limit of daily increment in serum sodium is not exceeded. Placed into a clinical perspective, even if a rapid correction is not always necessary, our results can help the physician to feel more comfortable with the therapeutic approach of the severe hyponatremic patients, knowing that, during the initial phase of the treatment, the serum sodium could be corrected rapidly without fear of permanent neurologic sequelae. This is more critical especially because some patients with severe symptomatic hyponatremia (precise duration of the electrolyte disturbance is frequently unknown) need prompt correction to avoid the possible dramatic consequences of untreated severe hyponatremia [1, 3, 11, 12, 14, 27]. In this situation the osmotic gradient produced by a rise in serum sodium lower than 4 mEq/liter, as proposed as a risk factor by Verbalis et al, perhaps is insufficient to significantly reduce brain edema. Moreover, in some cases, a spontaneous return of a normal diluting ability could induce an unpredictable rapid rise in serum sodium. One could also expect that, if brain damage was so strongly correlated with hourly changes in serum sodium (>4 mEq/liter/hr), myelinolysis should be more frequently encountered in the clinical setting [11].

We have employed in this work the currently used three-day model for chronic hyponatremia, which is of relatively short duration [6, 13, 14, 17–19, 23, 28] compared to the model used in the work of Verbalis et al where hyponatremia was maintained during 19 days [16]. However, if the chronicity of hyponatremia logically could enhance the brain susceptibility to the subsequent correction [6, 19, 28], after three days of hyponatremia the brain adaptative mechanisms to the hypoosmolar state have almost fully taken place [29, 30]. Therefore this would probably not explain the good tolerance to the aggressive regimen undergone by the rats in our study. By another way, we used in the present work AVP rather than DDAVP [16] to induce the hyponatremia. AVP use is in fact more physiological since vasopressin, unlike DDAVP, has specific effects on the V_1 receptors in the brain and could influence brain ion and volume homeostasis. From data obtained in Brattelboro rats [31] one could logically hypothesize that, in the presence of AVP, the brain will better support the osmotic stress related to the correction of the hyponatremia than the brain of DDAVP treated rats could do. Another risk factor which must be also considered during hyponatremia is related to the hypoxic-anoxic episodes which can occur as a

consequence of seizures and respiratory arrests. This complication which can lead to permanent brain damage is usually associated with acute hyponatremic state [27]. Likewise, it has been recently shown in rats that hypoxia may render the brain more susceptible to hypoxic injury and death [10]. If we have not observed episodes of convulsions in the present study, hypoxia cannot be completely excluded as a cause of brain damage in this chronic model [14]. Yet, several series of rats submitted to severe protracted hyponatremia failed to demonstrate any histological brain changes [13, 16, 18].

The second question considered in the present work was the influence of the correction methods and the associated degree of volume expansion on the outcome of hyponatremia. In several previous experimental works, different methods were used to correct the hyponatremic state (mainly i.p. NaCl, water restriction, water diuresis or urea) [13, 14, 16] but without considering the possibility that the way of correction by itself could contribute to the neuropathological sequelae. In our previous experiments [15, 21] we have demonstrated that urea, which efficaciously corrects hyponatremia [5, 32], induced a lower incidence and severity of brain lesions as compared to hypertonic saline when the rats were submitted to daily correction of serum sodium above the threshold of tolerance for the brain. Interestingly, the results of Verbalis et al [16] can be interpreted differently considering that brain damage occurred in animals which had high maximal rates of correction, and that most of them were treated with i.v. hypertonic saline, when rats without neuropathological sequelae presented low rates of correction but were corrected by water restriction alone [16]. The hypervolemia associated with NaCl infusion could have potential deleterious effect on the brain through hypothetical mechanisms like the increase in cerebral blood flow, an excessive water loss from the brain enhanced by the atrial natriuretic factor [33], or a direct ion-induced injury due to the overshoot of brain Na and Cl levels observed after NaCl administration [28].

The rats of group 1 were submitted to an acute and important osmotic stress (serum sodium rose 12 mEq/liter in 1 hr, range 8 to 17 mEq/liter) with a concomittant volume expansion, as illustrated by the significant fall in the hematocrit and plasma protein values. However, no difference could be observed in the outcome with group 2, where rats were corrected with a model of volume contraction through water restriction. The incidence of brain lesion was low in both groups (1 of 25 in group 1 and 2 of 24 in group 2) where the rats achieved daily change in serum sodium never exceeding 20 mEq/liter/24 hr. The neuropathological sequelae of a correction between 10 to 20 mEq/liter/24 hr are represented by 6% of damaged rats when the present series was pooled with our previous results [15] (6 of 96 rats, with 5 asymptomatic regaining weight, 4 out of them presenting only minor brain lesions; and 1 symptomatic animal). In clinical practice, however, this incidence of neurological complication is not negligible, and a more prudent approach would be to not exceed a serum sodium rise of 15 mEq/liter/day, an increment which can be made rapidly, if necessary.

Acknowledgments

This work was supported by a grant from the Fonds National de la Recherche Scientifque (F.N.R.S.) (1.5.204.91 F). A. Soupart is a recipient of a grant from the "Fondation Erasme." We gratefully acknowledge Mrs. M. Dierick for her technical assistance and Mrs. I. Mazza for her secretarial help. We are also indebted to Professor R. Heimann (Department of Pathology, Institut Jules Bordet, Free University of Brussels) and Professor R. Bellens for their continuous support.

Reprint requests to Dr. A. Soupart, Service de Médecine Interne, Hôpital Erasme, 808, Route de Lennik, 1070 Bruxelles, Belgium.

References

1. BERL T: Treating hyponatremia: Damned if we do and damned if we don't. *Kidney Int* 37:1006–1018, 1990
2. LAURENO R, ILLOWSKY BP: Pontine and extrapontine myelinolysis following rapid correction of hyponatremia. *Lancet* i:1439–1441, 1988
3. STERNS RH: The treatment of hyponatremia: first, do no harm. *Am J Med* 88:557–560, 1990
4. NARINS RG: Therapy of hyponatremia: Does haste make waste? *N Engl J Med* 314:1579–1580, 1986
5. SOUPART A: Optimal management of severe hyponatremia: A therapeutic dilemma. *Acta Clin Belg* 46:277–282, 1991
6. STERNS RH, THOMAS DJ, HERNDON RH: Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. *Kidney Int* 35:69–75, 1989
7. NORENBERG MD: Ultrastructural observations in electrolyte-induced myelinolysis. (abstract) *J Neuropathol Exp Neurol* 40:319, 1981
8. STERNS RH, THOMAS DJ, HERNDON RH: Osmotic demyelination syndrome (ODS): An experimental model. (abstract) *Kidney Int* 35:218, 1989
9. LIEN Y-HH, MARTIN DK: Potassium depletion is a predisposing factor for osmotic demyelination syndrome: A survival, histopathology and biochemistry study. (abstract) *J Am Soc Nephrol* 2(3):764, 1991
10. AYUS JC, GUNTUPALLI K, GUNTUPALLI J, KROTHAPALLI R: Effect of hypoxia in hyponatremic rats. (abstract) *Clin Res* 39(2):265A, 1991
11. AYUS JC, KROTHAPALLI RK, ARIEFF AI: Changing concepts in treatment of severe symptomatic hyponatremia. Rapid correction and possible relation to central pontine myelinolysis. *Am J Med* 78:897–902, 1985
12. AYUS JC, KROTHAPALLI RK, ARIEFF AI: Treatment of symptomatic hyponatremia and its relation to brain damage: A prospective study. *N Engl J Med* 317:1190–1195, 1987
13. AYUS JC, KROTHAPALLI RK, ARMSTRONG DL: Rapid correction of severe hyponatremia in the rat: Histopathological change in the brain. *Am J Physiol* 248:F711–F719, 1985
14. AYUS JC, KROTHAPALLI RK, ARMSTRONG DL, NORTON HJ: Symptomatic hyponatremia in rats: Effect of treatment on mortality and brain lesions. *Am J Physiol* 257:F18–F22, 1989
15. SOUPART A, STENUIT A, PERIER O, DECAUX G: Limits of brain tolerance to daily increments in serum sodium in chronically hyponatremic rats treated with hypertonic saline or urea: Advantages of urea. *Clin Sci* 80:77–84, 1991
16. VERBALIS JG, MARTINEZ AJ, DUTRAROSKY MD: Neurological and neuropathological sequelae of correction of chronic hyponatremia. *Kidney Int* 39:1274–1282, 1991
17. KLEINSCHMIDT-DEMASTERS BK, NORENBERG MD: Rapid correction of hyponatremia causes demyelination: Relation to central pontine myelinolysis. *Science* 211:1068–1070, 1981
18. KLEINSCHMIDT-DEMASTERS BK, NORENBERG MD: Neuropathologic observation in electrolyte-induced myelinolysis in the rat. *J Neuropathol Exp Neurol* 41:67–80, 1982
19. NORENBERG MD, PAPENDICK RE: Chronicity of hyponatremia as a factor in experimental myelinolysis. *Ann Neurol* 15:544–547, 1984
20. NORENBERG MD, LESLIE KO, ROBERTSON AS: Association between rise in serum sodium and central pontine myelinolysis. *Ann Neurol* 11:128–135, 1982
21. VAN REETH O, DECAUX G: Rapid correction of hyponatremia with urea may protect against brain damage in rats. *Clin Sci* 77:351–355, 1989

22. LAURENO R: Central pontine myelinolysis following rapid correction of hyponatremia. *Ann Neurol* 13:232–242, 1983
23. ILLOWSKY BP, LAURENO R: Encephalopathy and myelinolysis after rapid correction of hyponatremia. *Brain* 110:855–867, 1987
24. CHENG JC, ZIKOS D, SKOPICKI HA, PETERSON DR, FISHER KA: Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: The effect of rapid correction. *Am J Med* 88:561–566, 1990
25. TANNEAU R, GARRE M, PENNEC YL, JOUQUAN J, LEMENN G: Brain damage and spontaneous correction of hyponatremia. (letter) *Lancet* 2:1031–1032, 1988
26. WEISSMAN JD, WEISMAN BM: Pontine myelinolysis and delayed encephalopathy following rapid correction of acute hyponatremia. *Arch Neurol* 46:926–927, 1989
27. ARIEFF AI: Hyponatremia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 314:1529–1535, 1986
28. LIEN Y-HH, SHAPIRO JI, CHAN L: Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. *J Clin Invest* 88:303–309, 1991
29. POLLOCK AS, ARIEFF AI: Abnormalities of cell volume regulation and their functional consequences. *Am J Physiol* 239:F195–F205, 1980
30. VERBALIS JG, DRUTAROSKY MD: Adaptation to chronic hypoosmolality in rats. *Kidney Int* 34:351–360, 1988
31. DE PASQUALE M, PATLAK CS, CSERR HF: Brain ion and volume regulation during acute hyponatremia in Brattleboro rats. *Am J Physiol* 256:F1059–F1066, 1989
32. DECAUX G, UNGER J, BRIMIOULLE S, MOCKEL J: Hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone: Rapid correction with urea, sodium chloride and water restriction therapy. *J Am Med Assoc* 247:471–474, 1982
33. DOCZI T, JOO F, SZERDAHELYI P, BODOSI M: Regulation of brain water and electrolyte contents: The opposite actions of central vasopressin and atrial natriuretic factor. *Acta Neurochirugica* S43:186–188, 1988