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Brain dehydration and neurologic deterioration after rapid correction of hyponatremia

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Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. We made rats severely hyponatremic, varying the rate of onset and duration of the disturbance, and then compared rapid correction to slow correction. An acute fall in the plasma Na to 106 mEq/liter within seven hours caused seizures and coma, but these findings resolved and survival was 100% after either rapid or slow correction. A more gradual fall in plasma Na to 95 mEq/liter in three days caused neither seizures nor coma. Measurements of brain water and electrolytes showed that adaptive losses of brain Na and K (maximally depleted within seven hours) and slower losses of non-electrolyte solutes progressively reduced brain edema. After three days of hyponatremia, rapid correction to 119 mEq/liter with 1 M NaCl or to 129 mEq/liter by withdrawing DDAVP caused brain dehydration because lost brain K and non-electrolyte solutes were recovered slowly. This treatment was followed by a delayed onset of severe neurologic findings, demyelinating brain lesions and a mortality rate of over 40%. Slow correction (0.3 mEq/liter/hr) avoided these complications and permitted 100% survival. We conclude that the rat adapts quickly to hyponatremia and can survive with extremely low plasma sodium concentrations for prolonged periods. Although rapid correction is well tolerated when hyponatremia is of brief duration, it may cause brain damage in animals that have had time to more fully adapt to the disturbance.

Patients with severe hyponatremia may get worse neurologically after their electrolytes get better. This phenomenon, the "osmotic demyelination syndrome", has been attributed to rapid correction of chronic hyponatremia. To avoid this complication, some investigators have recommended that chronic hyponatremia should be corrected slowly, even when the plasma sodium concentration is extremely low [1, 2]. Others feel that the risks of continued severe hyponatremia outweigh the risks of rapid correction. This therapy, they argue, is necessary and safe as long as "overcorrection" to normonatremia or hypernatremia is avoided [3, 4].

The controversy is fueled by limitations in our current knowledge of the brain's capacity to respond to osmotic stress. The brain is known to lose solutes in response to hyponatremia, thereby limiting its absorption of water [5–13]. How successful is this adaptation in preventing injury from brain edema? Once the brain has adapted to severe hyponatremia, lost solutes must be recovered when the disturbance is corrected. Are these solutes recovered rapidly enough to insure against brain dehydration (and injury) when the plasma sodium concentration is suddenly returned towards normal? The present studies were designed to examine these questions in an experimental model.

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Methods

Male Sprague-Dawley rats (Holtzmann, Madison, Wisconsin, USA) weighing 265 to 315 g were studied. An antidiuretic state was induced either by the subcutaneous injection of vasopressin tannate in oil (Parke-Davis, Morris Park, New Jersey, USA), 1 unit daily, or (in studies in which an antidiuretic state was required for more than 24 hours) by the subcutaneous infusion of DDAVP (USV Laboratories, Tarrytown, New York, USA) with an Alzet osmotic minipump (Model 2001 or 2002, Alza, Palo Alto, California, USA) delivering a dose of 20 ng/hr. Unless otherwise stated, antidiuresis was maintained throughout the duration of the experiment. Hyponatremia was induced by administering electrolyte-free water by gavage and by allowing the animals access to 5% dextrose in water. No other food was provided during this phase of the experiment.

The rate of onset and duration of hyponatremia were varied so that three different groups of hyponatremic animals were studied; nine comparably treated normonatremic controls were studied concurrently for each experimental group.

Group I—(Rapid onset, 5 to 7 hours' duration). In 42 animals, water was administered in five equal hourly gavages (total dose = 15 ml/100 g body wt).

Group II—(Intermediate onset, 24 to 26 hours' duration). In another 42 animals, the same total dose of water was administered in five equal gavages given every two hours.

Group III—(Gradual onset, 72 to 74 hours' duration). In 99 animals, a low sodium and potassium tube feeding diet (ICN Nutritional Biochemicals, Cleveland, Ohio, USA) was administered for three days in four equal gavages daily delivering 12 ml/100 g body wt/day on the first two days and 8 ml/100 g body wt/day on the third day. Six of these animals were sacrificed after 24 hours and six after 48 hours of tube feedings to determine the rate of onset of hyponatremia.

Beginning five hours (Group I), 24 hours (Group II) or 72 hours (Group III) after the first gavage, all three groups were given intraperitoneal injections of saline (Fig. 1). The doses used (3 ml/100 g body weight in Groups I and II and 2 ml/100 g in Group III) were based on pilot studies and were intended to either leave the hyponatremia uncorrected (0.1 M NaCl) or to acutely increase the plasma sodium concentration by 25 mEq/

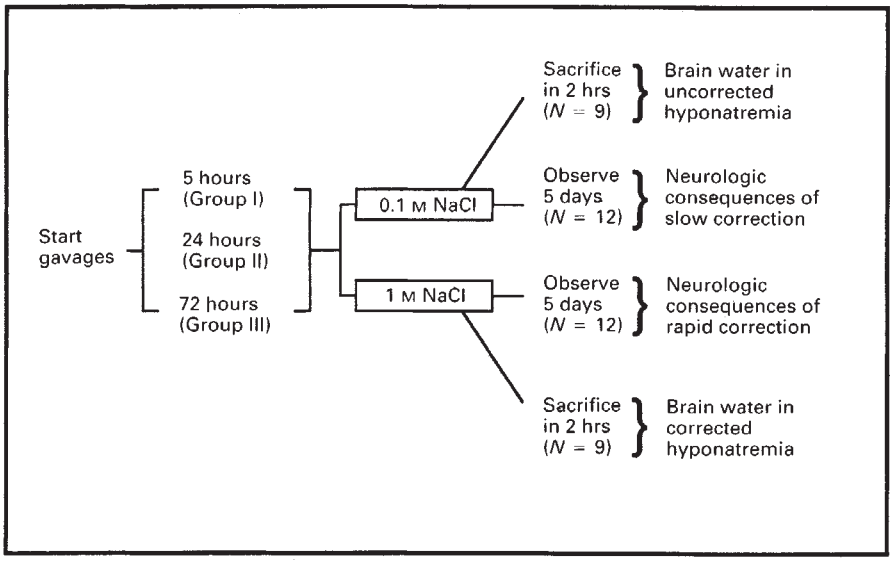

Fig. 1. *Experimental protocol.* As illustrated, 42 animals were studied in Groups I and II. A total of 99 animals were begun on the Group III protocol, of which 42 are illustrated here. Additional studies in Group III, not illustrated, include 31 animals in which withdrawal (or sham withdrawal) of DDAVP was substituted for the administration of 1 M NaCl, 25 that were studied to determine the rate of induction or correction of hyponatremia, and two that died in the attempt to maintain hyponatremia for three days.

liter (1 M NaCl). Normonatremic controls were given an equal volume of 0.15 M NaCl intraperitoneally. Two hours after these injections, the animals were either sacrificed for determinations of plasma sodium concentrations and brain water and electrolyte contents or observed for five days without handling to define the neurologic consequences of "slow" and "rapid" correction of hyponatremia (Fig. 1).

After receiving 0.1 M NaCl intraperitoneally, "slowly" corrected animals were fed a low sodium and potassium diet (ICN) and were given a solution of 5% dextrose in water to encourage fluid intake. After receiving 1 M NaCl, "rapidly" corrected animals were fed a regular diet and were allowed free access to drinking water. After five days of observation, surviving animals in each group were decapitated, blood was collected for plasma sodium concentrations, and the brains were removed and fixed in formalin for histologic examination by Dr. Herndon, who was unaware of the treatment the animals had received. Additional Group III animals (not illustrated in Fig. 1) were treated in the same manner and then sacrificed after 24 hours of observation to determine the rate of increase of the plasma sodium concentration after "slow" and "rapid" correction.

Because intraperitoneal 1 M NaCl corrects hyponatremia far more rapidly than would be achieved in a clinical setting, additional studies were done in Group III animals. In these studies, withdrawal of DDAVP for a period of nine hours was substituted for intraperitoneal 1 M NaCl. Afterwards, the animals were either sacrificed ($N = 9$) or the DDAVP infusion was resumed and continued for five days of observation ($N = 12$).

Analytical methods

In order to measure brain water and electrolyte contents, the animal was decapitated and the entire brain was rapidly removed. The cerebral hemispheres were then separated from the brain stem and cerebellum, weighed wet, and then reweighed after drying at 100°C to determine water content. The brain was then crushed and dissolved in 16 M HNO_3 and the sodium and potassium concentrations were measured by flame photometry (IL Model 443, Boston, Massachusetts, USA). The results were expressed per kg dry brain weight.

Calculations

Changes in the brain's total solute content were calculated from the observed changes in plasma sodium concentration and brain water content, making the assumption that osmotic equilibrium is attained between brain and plasma water [9, 10].

Statistical methods

Data are expressed as mean values ± SEM. Differences between groups were assessed by one factor ANOVA with significance determined by the Scheffe F-test (Statview 1.1 Brain Power, Calabasas, California, USA) and accepted at the $P < 0.05$ level.

Results

In Group I, the plasma sodium concentration fell to 106 ± 2.1 mEq/liter within five to seven hours. In Group II, this severity of hyponatremia was achieved within nine to eleven hours, and by 26 hours the plasma sodium concentration had reached 95 ± 0.8 mEq/liter. Hyponatremia developed more gradually with the Group III protocol: by 24 hours the plasma sodium concentration was 115 ± 2.0 mEq/liter, at 48 hours it was 105 ± 3.0 mEq/liter, and by 74 hours it had reached 95 ± 0.7 mEq/liter.

Despite extremely low plasma sodium concentrations, no deaths occurred during the induction of hyponatremia among the 42 Group I animals or the 42 Group II animals, and only 2 of 87 Group III animals died in the attempt to maintain hyponatremia for three days.

The animals' neurologic condition depended on how rapidly their hyponatremia had developed. Group I animals which were made hyponatremic with five hourly gavages were stuporous or semicomatose and 19% were noted to have tonic-clonic seizures. Group II animals that became profoundly hyponatremic within 24 hours were stuporous but arousable, and seizures were not observed. Group III animals that became profoundly hyponatremic over the course of 72 hours remained awake and

Table 1. Brain water and electrolyte contents: Non-hyponatremic controls

	Group I	Group II	Group III
Plasma sodium *mEq/liter*	138 ± 2.5	141 ± 0.6	144 ± 0.9
Brain water *liter/kg*	3.86 ± 0.032	3.78 ± 0.015	3.84 ± .015
Brain sodium *mEq/kg*	198 ± 7.7	198 ± 2.4	208 ± 1.9
Brain potassium *mEq/kg*	460 ± 14.2	457 ± 4.7	473 ± 2.3
Brain Na + K *mEq/kg*	657 ± 21.2	655 ± 6.9	682 ± 3.9

Table 2. Brain water and electrolyte contents: Untreated hyponatremia

	Duration of hyponatremia		
	Group I 7 hours	Group II 26 hours	Group III 74 hours
Plasma sodium *mEq/liter*	106 ± 2.1[a]	95 ± 0.8[a]	95 ± 0.7[a]
Brain water in *liter/kg*	4.27 ± 0.030[a]	4.06 ± 0.017[a]	4.03 ± 0.020[a]
(% of control)	(110.6%)	(107.5%)	(104.6%)
Brain sodium in *mEq/kg*	143 ± 5.0[a]	150 ± 1.7[a]	163 ± 1.6[a]
(% of control)	(72%)	(76%)	(78%)
Brain potassium in *mEq/kg*	399 ± 13.0[b]	387 ± 4.3[a]	399 ± 3.3[a]
(% of control)	(87%)	(85%)	(84%)
Brain Na + K in *mEq/kg*	542 ± 17.3[b]	537 ± 5.8[a]	562 ± 4.8[a]
(% of control)	(83%)	(82%)	(82%)

[a] $P < 0.001$ vs. control
[b] $P < 0.01$ vs. control (see Table 1)

without seizures throughout the induction of hyponatremia, but they were somewhat sluggish in their movements. Because these animals were tube fed, they gained 0.6% of their body weight during induction of hyponatremia, and their normonatremic controls lost only 5% of their weight.

Brain water and electrolyte contents

Brain water and electrolyte contents in non-hyponatremic controls are shown in Table 1.

Uncorrected hyponatremia. The values for hyponatremic animals sacrificed two hours after receiving 100 mM NaCl are shown in Table 2. In all three hyponatremic groups, brain water contents were significantly greater than in controls, but the percentage increase was considerably less than the percentage decrease in plasma sodium concentration. Brain edema became increasingly less severe in the groups with more prolonged hyponatremia (Fig. 2).

As expected, brain sodium and potassium contents fell in response to hyponatremia (Table 2). However, the loss of these solutes was no less in Group I animals (with only 7 hours of hyponatremia) than in Groups II and III (with 26 and 74 hours of hyponatremia). Hence, progressive losses of brain electrolyte could not account for the decreasing severity of brain edema; non-electrolyte solutes must have been lost from the brain (or osmotically inactivated), contributing to the adaptive defense against osmotic brain edema (Fig. 2).

Rapidly corrected hyponatremia. Within two hours after the administration of hypertonic saline, the plasma sodium concentration had increased by 25 mEq/liter to mildly hyponatremic levels, and brain water content had decreased in all three hyponatremic groups (Table 3). In Groups I and II, brain water content returned to values statistically indistinguishable from controls. However, in Group III, significant brain dehydration occurred (Table 3, Fig. 3). Brain sodium content returned to control levels in all three groups, but brain potassium content remained low in Groups II and III (Table 3). Similarly, in Group II and, to a greater extent in Group III, non-electrolyte solute (a calculated value) also remained below control levels after treatment (Fig. 3). Thus, in chronic hyponatremia, slow recovery of lost brain potassium and non-electrolyte solute makes brain cells susceptible to dehydration when the disturbance is rapidly corrected with hypertonic saline even when the plasma

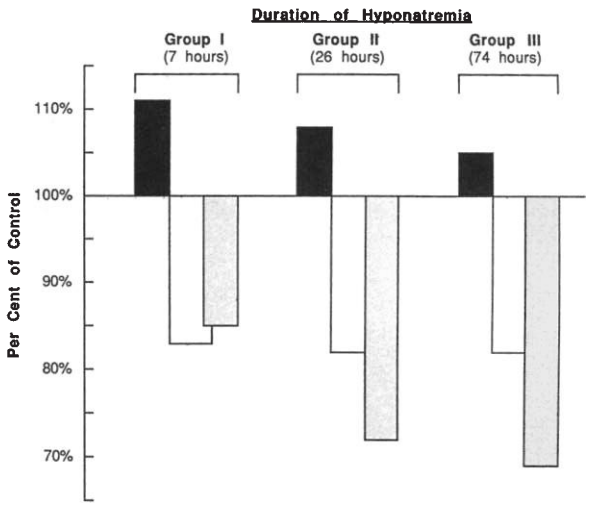

Fig. 2. *Brain water (■), sodium and potassium contents were measured two hours after an intraperitoneal injection of 0.1 M saline to animals that had been hyponatremic for 7 hours (Group I), 26 hours (Group II) or 74 hours (Group III).* It is assumed that this injection did not alter the plasma sodium concentration and merely prolonged the disturbance for an additional two hours (see Table 2). Total brain solute (▩) was calculated from the measured increase in brain water and the measured decrease in plasma sodium concentration. Symbol (□) is brain cation content.

Table 3. Brain water and electrolyte contents after treatment with hypertonic saline

	Duration of hyponatremia before correction		
	Group I 5 hours	Group II 24 hours	Group III 72 hours
Plasma sodium *mEq/liter*	131 ± 0.8[a]	124 ± 1.9[a]	119 ± 1.6[a]
Brain water in *liter/kg*	3.90 ± 0.033	3.76 ± 0.022	3.76 ± 0.020[b]
(% of control)	(101.0%)	(99.3%)	(97.8%)
Brain Na in *mEq/liter*	180 ± 9.6	201 ± 5.0	199 ± 4.6
(% of control)	(91%)	(102%)	(96%)
Brain K in *mEq/kg*	427 ± 11.8	407 ± 9.4[b]	406 ± 5.6[a]
(% of control)	(93%)	(89%)	(86%)
Brain Na + K in *mEq/kg*	607 ± 21.0	608 ± 14.5[a]	605 ± 8.7[a]
(% of control)	(92%)	(93%)	(89%)

[a] $P < 0.001$ vs. control
[b] $P < 0.01$ vs. control (see Table 1)

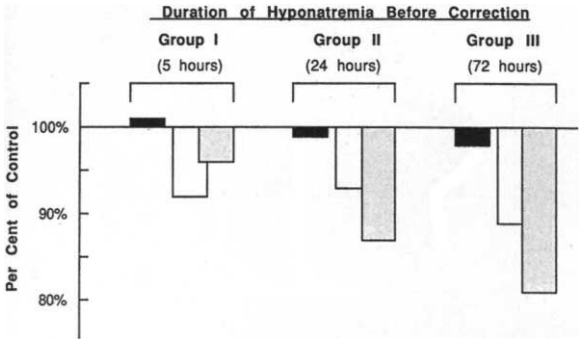

Fig. 3. *Brain water (■), sodium and potassium contents were measured two hours after administration of 1 M NaCl to Groups I, II and III (Table 3).* Total brain solute (▩) was calculated from the change in brain water and plasma sodium concentration as compared to control levels. Symbol (□) is brain cation content.

sodium concentration is increased to mildly hyponatremic levels.

Brain dehydration was also demonstrable in Group III animals in which the plasma sodium concentration was allowed to increase spontaneously after withdrawal of DDAVP. An increase in plasma sodium from 98 ± 2.3 to 129 ± 1.4 mEq/liter over nine hours (an average increase of 3.4 mEq/liter/hour) resulted in a brain water content that was 2% below control levels (3.69 ± 0.016 vs. 3.76 ± 0.017 liter/kg dry wt, $P < 0.001$). At this time, brain potassium content was still 7% lower than that in controls (425 ± 4.5 vs. 457 ± 8.1 mEq/kg, $P < 0.01$); but brain sodium content had become 10% higher than controls (234 ± 3.6 vs. 213 ± 2.9 mEq/kg, $P < 0.001$). As total brain cation content had returned to control levels, slow recovery of non-electrolyte solute, as well as potassium, must be invoked to explain the observed brain dehydration.

Therapeutic outcome after correction of hyponatremia

Animals that had been hyponatremic for 24 hours or less did well regardless of how rapidly their electrolyte disturbance was corrected. All Group I animals and all but two Group II animals survived without any neurologic abnormalities after both rapid and slow correction. Remarkably, the slowly corrected Group I animals recovered from seizures, stupor and coma despite a minimal increase in their plasma sodium concentration; after five days of observation, the plasma sodium concentration in this group was 111 ± 2 mEq/liter.

By contrast, the rate of correction of hyponatremia in the Group III animals had a dramatic effect on both neurologic morbidity and mortality; animals corrected "slowly" by evaporative water losses fared much better than those corrected "rapidly" by the administration of hypertonic saline or by the withdrawal of DDAVP (Fig. 4).

In Group III animals corrected rapidly with a single injection of hypertonic saline (thereby increasing the plasma sodium to 119 mEq/liter within two hours), the animals initially improved neurologically, becoming more active than they had been when severely hyponatremic. However, one day later, obvious and severe neurologic deterioration (seizures, marked gait disturbances, stupor and coma) became apparent, and one of the animals died. In five animals sacrificed at the onset of these findings, the plasma sodium concentration averaged 129 mEq/liter with a range of 121 to 138 mEq/liter. Thereafter, all but one of the 12 remaining animals became neurologically impaired, and by the fifth day of observation five of them had died. The surviving animals did not seek the water available to them and therefore, despite continued infusion of DDAVP, they became hypernatremic (158 ± 4 mEq/liter) at five days. The brains of the survivors showed widespread areas of disruption and vacuolization of myelin, particularly marked in the corpus callosum and striatum; neurons in the cerebral cortex, hippocampus and basal ganglia all appeared normal. Histologic findings were minimal in the one animal that remained in good condition throughout the period of observation.

The twelve Group III animals corrected rapidly by withdrawal of DDAVP had a similar course. After initial correction to mild hyponatremia (129 ± 1.4 mEq/liter at 9 hrs), the animals became more active. Within one to two days of correction, however, 10 of the 12 animals observed had deteriorated neurologically and by five days (when the plasma sodium concentration of the survivors was 143 ± 4.8 mEq/liter), seven of the animals had died.

In slowly corrected Group III animals, the plasma sodium concentration increased by an average of 8 mEq/liter/day. All of these animals steadily improved and those that were observed for five days survived in good condition. The histologic appearance of the brains of these animals reflected their neurologic condition; no disruption of myelin was seen.

Discussion

The adaptation to severe hyponatremia is extremely efficient in the rat. We reduced the plasma sodium concentration to 106 mEq/liter in five to seven hours; although neurologic manifestations were severe, mortality was nil, even when the disturbance remained virtually uncorrected for five days. Not surprisingly, a more gradual onset of hyponatremia was even better tolerated, with more moderate neurologic findings, despite a plasma sodium concentration of 95 mEq/liter. All these animals also survived without neurologic sequelae when severe hyponatremia was corrected slowly over the course of several days; on the other hand, rapid correction to mildly hyponatremic levels was followed by delayed neurologic deterioration and over 40% of the animals died. In chronic hyponatremia, the treatment was clearly worse than the disease.

The rat's remarkable tolerance for slowly evolving severe hyponatremia has been noted by three other groups of investigators [13–18]. Similarly, recent studies have shown that most patients tolerate extremely severe hyponatremia and that vigorous therapeutic efforts are seldom needed to ensure their survival [1, 2].

Acute water intoxication can, of course, be fatal. Patients may die of transtentorial herniation of the brain if the plasma sodium concentration becomes low enough within a short enough time (less than 24 hours in most reported cases) [4, 19]. An extremely abrupt onset of hyponatremia can also be fatal in experimental animals. Arieff, Llach and Massry have shown that when the plasma sodium concentration of rabbits was reduced by over 20 mEq/liter in less than two hours, 86% of the animals died [5]. Others have reported a high mortality rate when severe hyponatremia was induced with large boluses of

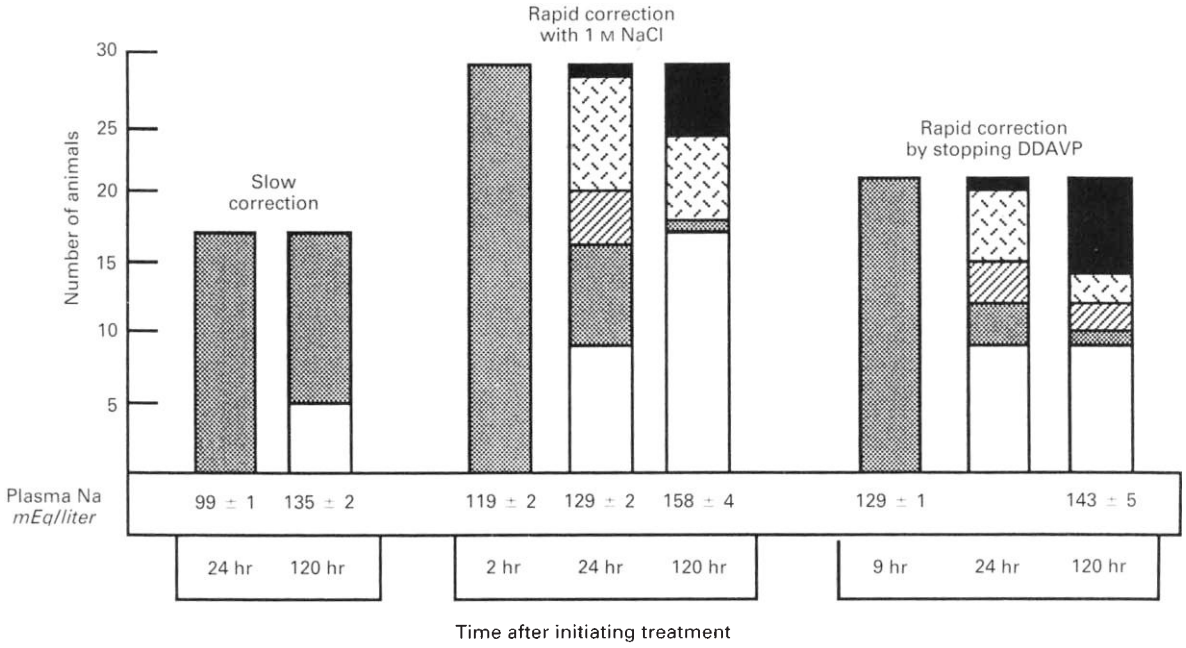

Fig. 4. *Neurologic findings in animals made hyponatremic over 72 hours and then corrected slowly or rapidly (with intraperioneal 1 M NaCl or by the temporary withdrawal of DDAVP).* Following these maneuvers, both slowly and rapidly corrected groups continued to receive DDAVP and had free access to water. After rapid correction with 1 M NaCl, animals became neurologically impaired while still mildly hyponatremic and failed to seek water. Therefore, they became hypernatremic at 120 hours. Animals were sacrificed 2 hours and 24 hours after 1 M NaCl and 9 hours after withdrawal of DDAVP for plasma sodium determinations, reducing the number under observation. Symbols are: (□) sacrificed for plasma; (▩) awake and active; (▨) awake but lethargic; (▧) convulsing or stuperous; (■) fatal neurologic complications.

free water given with anesthetics [20, 21]. Clearly, the adaptation to acute hyponatremia has limits.

The brain loses solutes in response to hyponatremia, thereby limiting its absorption of water. Sodium losses begin almost immediately [10] and potassium losses can be demonstrated within three to four hours [8–10]. However, there appears to be a limit to these solute losses. In our studies, cation losses became maximal by seven hours and remained at 82 to 83% of control levels regardless of whether the disturbance had been present for 7 or 74 hours and whether the plasma sodium concentration was 106 or 95 mEq/liter. Four other laboratories have reported nearly identical losses of brain cation in rats with plasma sodium concentrations ranging from 110 to as low as 72 mEq/liter [6, 7, 11, 13].

When the plasma sodium concentration is extremely low, defense of brain volume depends on losses of non-electrolyte solute. This process, which begins later and proceeds more slowly than losses of brain cation, allows brain water contents to gradually return towards normal. An accumulation of such solutes (often referred to as "idiogenic osmoles") has long been recognized in animals adapting to hypernatremia, but until recently, their role in the adaptation to hyponatremia has not been emphasized [9].

Recent evidence suggests that "idiogenic osmoles" are largely amino acids [12, 22]. Thurston has shown in weanling mice that the brain amino acid content falls by approximately 50% after three days of severe hyponatremia (plasma sodium 110 mEq/liter). The osmotic contribution of the lost amino acids is large enough to account for most of the calculated losses of non-electrolyte solute in our studies.

While adaptive solute loss from the brain defends against cerebral edema in severe hyponatremia, it also increases the brain's susceptibility to dehydration when the plasma sodium concentration is returned to normal [12, 13]. With time, the brain becomes increasingly vulnerable to this complication because solutes that are lost most slowly during the adaptation are also recovered most slowly during correction of the disturbance.

We find that brain sodium is recovered extremely rapidly during correction of hyponatremia. (This may be analogous to the rapid increase in brain sodium that occurs when an animal is made hypernatremic—a process recently shown to reflect bulk flow of sodium-rich fluid into the brain through anatomic communications between the cerebrospinal fluid and the brain's interstitial space [23].) Potassium and non-electrolytes (presumably cellular solutes) are recovered more slowly than sodium. Consistent with our studies, Dila and Pappius [6] reported low brain potassium contents 24 hours after correction of chronic hyponatremia in the rat, and Thurston [12] reported low levels of brain amino acids nine hours after correction of chronic hyponatremia in the mouse.

Our studies confirm and extend those of Verbalis, Baldwin and Robinson [13] and Thurston [12], and show that the brain becomes dehydrated after rapid correction of hyponatremia even when the plasma sodium concentration remains in the mildly hyponatremic range after treatment. This can occur at rates of correction that are disturbingly close to what has been recommended clinically.

Measurements of total brain water (representing both extracellular and intracellular water) may underestimate the true

severity of cellular dehydration, because brain sodium contents (likely to reflect extracellular fluid) are recovered rapidly and sometime rise above control levels. Moreover, all brain cells do not swell equally in hyponatremia [24] and may not necessarily recover solutes at equal rates; selected cells may be particularly vulnerable to dehydration and injury after rapid correction of the disturbance.

Brain dehydration after rapid correction of hyponatremia does not cause immediate neurologic findings. In fact, the neurologic condition of chronically hyponatremic animals initially improved after the plasma sodium concentration was increased into the mildly hyponatremic range. However, this improvement was followed by severe neurologic findings at a time when the plasma sodium concentration was still low. As others have shown [15–17, 20, 21, 25, 26], this delayed neurologic deterioration is associated with demyelinating brain lesions. The same sequence has also been described in rats, rabbits, and dogs [15–17, 20, 21, 25] and it closely resembles the "osmotic demyelination syndrome" in humans [1, 2, 26]. The experimental findings support the idea that this syndrome is a complication of the rapid treatment of hyponatremia [1, 2, 26], not of anoxic insults resulting from hyponatremia itself [4, 19].

In our studies, brain dehydration occurred because of an increase in plasma sodium concentration that was *rapid* enough to outpace the recovery of solutes lost during the adaptation to hyponatremia and *large* enough to osmotically "shrink" cells at a time when their solute content was reduced. The ensuing neurologic deterioration did not develop until one to two days after this abrupt increase in sodium concentration (at a time when the magnitude of correction was several mEq/liter greater), and demyelinating lesions were not documented until five days later (at a time when the animals had become hypernatremic because of their inability to seek water). One might, therefore, attribute brain injury to the magnitude of correction that had taken place at the time that these adverse consequences became evident. However, in preliminary studies, we have shown that histologic injury begins in our model immediately after the administration of 1 M NaCl or withdrawal of DDAVP and that the neurologic manifestations of injury are delayed, even when the plasma sodium concentration is held constant after these maneuvers [27].

While our studies demonstrate that delayed neurologic deterioration and demyelinating brain lesions can be caused by a large rapid increase in the plasma sodium concentration, they leave unanswered the question of precisely how rapidly or by how much it must be increased before these complications develop. The threshold for causing injury would be likely to vary depending on the severity and duration of hyponatremia before it was corrected. Moreover, the threshold for the rat might not necessarily be applicable to humans.

The rat is extremely tolerant of rapid changes in sodium concentration: we found no sequelae after a 32 mEq/liter *decrease* over five hours in normonatremic animals, or a 25 mEq/liter *increase* over two hours in acutely hyponatremic animals. Humans are unlikely to experience, let alone survive, osmotic stresses this severe. It is therefore remarkable that after three days of hyponatremia, fatal injury occurred after the plasma sodium concentration of the rat was increased by 31 mEq/liter over nine hours. This rate of correction can be easily achieved in a clinical setting, and it does not always result in brain damage [1–4, 28–31]. Indeed, there are several published reports in which severely hyponatremic patients recovered uneventfully after receiving virtually the same rate and magnitude of correction that was lethal to our animals [29–31]. These reports have been cited to bolster the argument that "rapid" correction of hyponatremia is "safe" [3, 4, 19, 28]. Our experimental studies, like those of Norenberg [17], and recent clinical observations in humans [2] illustrate the difficulties with this interpretation: the susceptability to therapeutic injury in hyponatremia increases with the chronicity of the electrolyte disturbance. Thus, therapy that is benign in one patient may prove disastrous in another.

The fact that a large, rapid increase in the plasma sodium concentration is sometimes well tolerated does not mean that such treatment is necessary. In clinical situations, hyponatremia has usually been present for a considerable length of time before neurologic symptoms develop and before the reason for these symptoms is recognized [2]. During this time, an ongoing adaptation progressively reduces the severity of cerebral edema. Consequently, severely symptomatic patients, like severely symptomatic animals, can survive without apparent sequelae, even when their electrolyte disturbance is allowed to correct extremely slowly [1, 2]. The adaptation that makes this possible is the patient's ally; it can also be the therapist's foe. The clinician may choose to urgently elevate the plasma sodium concentration so as to further minimize cerebral edema or to stop convulsions. While such therapy will undoubtedly relieve symptoms, it will also entail some risk. The minimum increment in sodium concentration capable of producing therapeutic complications has not been and probably cannot be defined, but it has been estimated to be as little as 12 mEq/liter/day [1, 2]. More rapid rates of correction increase the risk for iatrogenic injury and have not been shown to improve the patient's chances for recovery [1, 2].

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