ELSEVIER

Brain Research 852 (2000) 167–172

BRAIN RESEARCH

www.elsevier.com/locate/bres

Research report

Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia

A. Soupart [a,d,*], R. Penninckx [c], A. Stenuit [a], G. Decaux [a,b]

[a] *Research Unit for the Study of Hydromineral Metabolism, Erasmus University Hospital, Free University of Brussels, Brussels, Belgium*
[b] *Department of Internal Medicine, Erasmus University Hospital, Free University of Brussels, Brussels, Belgium*
[c] *Laboratory of Chemical Biology, Erasmus University Hospital, Free University of Brussels, Brussels, Belgium*
[d] *Department of Internal Medicine, Jolimont-Tubize, Belgium*

Accepted 26 October 1999

Abstract

Brain myelinolysis complicates excessive correction of chronic hyponatremia in man. Myelinolysis appear in rats for correction levels ΔSNa) > 20 mEq/l/24 h. We previously showed in rats that when chronic hyponatremia was corrected with urea, the incidence and the severity of brain lesions were significantly reduced compared to hypertonic saline. In man, hyponatremia is frequently associated with azotemia and hemo-dialysis usually corrects rapidly the serum sodium (SNa) but only few patients apparently develop demyelination. We hypothesize that uremic state protects brain against myelinolysis. This hypothesis was evaluated in rats developing azotemia by administration of mercuric chloride ($HgCl_2$, 1.5 mg/kg). Severe (SNa < 120 mEq/l) hyponatremia (3 days) was induced by S.C. AVP and i.p. 2.5% D-glucose for 3 days. $HgCl_2$ was injected on day 2. Hyponatremia was corrected on day 4 by i.p. injections of 5% NaCl in order to obtain a correction level largely above the toxic threshold for brain (ΔSNA ~ 30 mEq/l/24 h). Surviving rats were decapitated on day 10 for brain analysis. In the group with renal failure (Group I, $n = 15$, urea 59 mmol/l) the outcome was remarkably favourable with only three rats (3/15) dying before day 10 and only one of them (1/3) presenting myelinolysis-related neurologic symptoms. The 12 other rats (80%) survived in Group I without symptoms and brain analysis was normal in all of them despite large correction level (ΔSNa: 32 mEq/l/24 h). On the contrary in nine rats in which $HgCl_2$ did not produce significant azotemia (control 1, $n = 9$, urea: 11 mmol/l), all the rats developed severe neurologic symptoms and eight of them died before day 10. Similar catastrophic outcome was observed in the non-azotemic controls (control 2, no $HgCl_2$ administration, $n = 15$, urea: 5 mmol/l). All of them developed myelinolysis-related neurologic symptoms and only four of them survived with severe brain lesions (survival 12/15 in Group I vs. 5/24 in pooled controls 1 and 2, $p < 0.001$). In conclusion, we showed for the first time that chronic hyponatremic rats with azotemia (48 h) tolerated large increases in SNa (~ 30 mEq/l/24 h) without significant brain damage.

Keywords: Renal failure; Central pontine myelinolysis; Osmotic stress; Urea; Blood-brain-barrier

1. Introduction

Brain myelinolysis (central pontine and extrapontine myelinolysis) is a well-recognized complication of inappropriate (excessive) correction of chronic (> 48 h) hyponatremia in human. Animal experiments obviously demonstrated the strong association between critical daily level of serum sodium (SNa) correction (ΔSNa > 20–25 mEq/l/24 h in rats) and the development of myelinolytic lesions [10,19,25,31].

The definite (cellular) mechanisms responsible for the development of the demyelinating process after an osmotic stress is still an unresolved question.

Nevertheless, the most likely scenario implicates an excessive brain dehydration as the first step of these pathologic process.

Adaptative mechanisms allow brain to limit its volume change when faced to an osmotic stress. Brain solute content decreases (within 24–48 h) during hyponatremia (to avoid excessive edema) and the osmolytes lost initially are regained subsequently during serum sodium correction to avoid brain shrinking [19].

The relatively slow (5 to 7 days) recovery of the initial solute content during the correction phase explains why

* Corresponding author. Unité de Recherche du Métabolisme Hydrominéral, Département de Médecine Interne, Hôpital Erasme, 808, route de Lennik, 1070 Bruxelles, Belgium. Fax: +32-2-555-32-11.

0006-8993/00/$ - see front matter
PII: S0006-8993(99)02259-3

brain is exposed to an excessive dehydration when the SNa is abruptly increased during chronic hyponatremia.

Excessive water shift out of the brain tissue is followed by a sequence of events (osmotic opening of the blood-brain-barrier (BBB) with influx of myelinotoxic factors, rapid accumulation of hypertonic edema fluids, intracellular hyperionisation) which are probably responsible for further oligodendrocytes degeneration and consequently for demyelination [19]. Recent observation made in rats suggest that activation of complement after disruption of the BBB is probably involved in the genesis of the brain lesions [30].

One must remember that the outcome of patients with myelinolysis could be dramatic with major functional sequelae or death [8] and there is actually no treatment available for this demyelinating process.

Two different experimental approaches from this laboratory provides encouraging results in an attempt to minimize or to prevent brain damage caused by inappropriate correction of chronic hyponatremia.

In the first one, we showed that relowering the SNa in the first hours or days after overzealous correction of hyponatremia prevents the development of myelinolysis in asymptomatic rats and reduces the incidence of neurologic complications and death in animals with pre-existing neurologic signs and symptoms [18,20]. We suggest that brain rehydration could interrupt the demyelinating process. In human, this therapeutic maneuver could also be safely achieved for potential prevention of myelinolysis [22].

In the second one, we demonstrated that when urea was used to correct chronic hyponatremia in rats, risk of brain damage was significantly reduced as compared to treatment with hypertonic saline [17].

How exactly exogenous urea, currently used in clinical settings to treat hyponatremia [3–5,19], is acting to protect brain is still not elucidated.

Hyponatremia is a common problem in patients with renal failure and hemodialysis usually rapidly elevates the serum sodium concentration. However, despite a large number of published cases, myelinolysis has been very rarely reported in uremic patients with hyponatremia after dialysis.

Therefore, given our previous observations we hypothesize that azotemia could afford some protection for brain during rapid correction of hyponatremia in patients with renal failure.

In the present work, we evaluate whether the risk of neurological complications and death after large correction of chronic hyponatremia is reduced in rats with associated acute renal failure.

2. Materials and methods

Male Wistar rats weighting 200 to 250 g were used in the experiments. Rats were housed in individual cages and were allowed to adapt for 3 days before starting the study. They were maintained on a standard diet of pelleted rat chow and were given free access to water. Mean temperature was controlled (25°C) with lights on from 0700 to 1900 h. During all the experiments, adequate measures were taken to minimize pain or discomfort.

2.1. Induction of chronic severe hyponatremia (day 1 to day 3)

In all the animals, chronic (3 days) severe (SNa < 120 mEq/l) hyponatremia was induced by the administration of arginine-8-vasopressin, infused continuously at a rate of 24 mU/h through subcutaneous osmotic minipumps (model 2001; ALZET, Palo Alto, CA) implanted under light ether anesthesia along the back at least 4 h before intraperitoneal (i.p.) injection of 2.5% (140 mM) D-glucose in water [20,28]. Animals received i.p. injections of D-glucose equivalent to 5% initial body weight twice daily on days 1 and 3 (0900 and 1700 h) and once daily on day 2 (1200 h) [17].

2.2. Induction of renal failure (Group I and control 1)

Azotemia was obtained in Group I ($n = 15$) by administration of a solution of mercuric chloride ($HgCl_2$). $HgCl_2$ was injected subcutaneously on day 2 (0900 h) at a dose of 1.5 mg/kg (in 1 ml of distilled water) [7,13].

This single sublethal dose was used to obtain a reversible renal failure allowing rats to survive up to day 10 [13].

As described previously, some rats did not develop significant azotemia (arbitrarily defined as blood urea levels > 16 mmol/l) despite $HgCl_2$ administration. These rats represent the first control group (control 1, $n = 9$). Another group did not receive $HgCl_2$ during the hyponatremic phase and represents the ''non-uremic'' controls (control 2, $n = 15$).

Rats with urea levels > 100 mmol on day 4 were excluded in order to avoid rats dying from severe azotemia before day 10.

2.3. Correction of hyponatremia (day 4)

In each group (Group I, controls 1 and 2), hyponatremia was corrected on day 4 by intraperitoneal injections of hypertonic saline.

All the rats received one injection (1200 h) of 1 M NaCl at a dose of 2.5 ml/100 g body weight. This dose of NaCl was determined to obtain a gradient of serum sodium largely above the threshold of 20 mEq/l/24 h required to induce brain lesions in non-uremic rats [17]. AVP infusion was continued throughout all the experiment. During the subsequent days up to day 10, the behavioural abnormalities were noticed and the day of the death was recorded for each rat (the day 1 corresponding to the first day of the

experiment). The number of surviving rats on day 10 were compared between each group.

Blood samples (0.25 ml) were collected via repeated tail transections under light ethyl-ether anesthesia for serum sodium (ion-selective analyses, Microlyte; Kone, Espoo, Finland), urea and creatinine (ABL 500; Radiometer, Copenhagen, Denmark) and osmolality measurements (Auto-stat, Model OM-6030 AKRAY-Menarini).

The serum sodium creatinine and urea concentrations were determined on day 4 (at the time of hyponatremia and after 48 h of azotemia) and on day 5 (24 h after NaCl administration and after 72 h of azotemia). In some additional rats in each group serum osmolality was also measured on days 4 and 5.

Rats had free access to food and water from day 4 to the time of their death (day 10).

2.4. Histological examination of the brains

At day 10 of the experiment, all surviving rats were sacrificed. They were decapitated and the brains were removed and placed immediately in 10% buffered formaldehyde for 10 days. In rats found dead in their cages before day 10, brain examination was not performed to avoid problem of autolysis artefacts in brain analysis [17,28]. Brains were sectioned coronally at six levels and processed for light microscopy as previously described [17].

Briefly, sections were stained with hematoxylin-eosin for evaluation of neuronal density and Luxol Fast blue for analysis of myelin integrity. Sections were interpreted by a neuropathologist (AST) without knowledge of the treatment groups of the animals.

2.5. Statistical analysis

Values are expressed as mean ± S.D. To determine statistical differences of various parameters between different groups, *t*-test, paired *t*-test and the chi-square test were used as appropriate.

3. Results

The results of the kinetic of serum sodium, urea values and the outcome of the rats in each group are presented in Table 1.

All the rats developed severe hyponatremia (SNa < 120 mEq/l) with no significant differences between each group. No mortality was associated with the induction phase of the hyponatremia.

After administration of $HgCl_2$ (Group I and control 1), 15 rats (Group I) developed significant renal failure with a slight additional increase in urea levels between day 4 (urea: 59 ± 15 mmol/l, creatinine: 0.32 ± 0.13 mmol/l) and day 5 (urea: 73 ± 27 mmol/l, creatinine: 0.36 ± 0.19 mmol/l).

In nine rats (control 1), $HgCl_2$ administration was not followed by significant azotemia (arbitrarily defined as urea levels > 16 mmol/l). The mean values of urea concentration was 11 ± 5 mmol/l and creatinine 0.06 ± 0.01 mmol/l ($n = 9$).

Ten rats were excluded because of very high levels of urea on day 4 (mean urea levels of 117 ± 10 mmol/l and creatinine 0.5 ± 0.1 mmol/l). All of them became severely apathic and comatous and all were dead after 48 h.

Table 1
Outcome of hyponatremic rats with or without azotemia after excessive (ΔSNa ≥ 25 mEq/1/24 h) correction of the serum sodium

Mean ± S.D.	Hyponatremia (day 4)			24 h after NaCl (day 5)			Outcome
	SNa (mEq/l)	Urea (mmol/l)	OSM_1[a] (mosM/kg H_2O)	ΔSNa (mEq/l)	Urea (mmol/l)	OSM_2[a] (mosM/kg H_2O)	Rats surviving on day 10
Group I ($HgCl_2$) (azotemia, $n = 15$)	105 ± 8	59 ± 15	290 ± 21 ($n = 7$)	32 ± 5	73 ± 27	368 ± 27 ($n = 7$)	12/15*
Range	(90–119)	(22–78)		(25–45)	(17–98)		
Control 1 ($HgCl_2$) (no significant azotemia, $n = 9$)	109 ± 6	11 ± 5	236 ± 11 ($n = 6$)	29 ± 3	8 ± 3	286 ± 21 ($n = 6$)	1/9
Range	(95–114)	(3–16)		(26–35)	(3–14)		
Control 2 (no azotemia, $n = 15$)	105 ± 6	5 ± 0.6	229 ± 10 ($n = 6$)	29 ± 4	–	278 ± 16 ($n = 6$)	4/15
Range	(94–116)	(3–6)		(25–36)			

* $p < 0.001$ as compared to control 1 and < 0.005 to control 2.
[a] Osmolality for each group was measured in additional rats not included in the other results.
Control 1: no significant azotemia despite $HgCl_2$ administration.
Control 2: hyponatremia without renal failure (no $HgCl_2$).
SNa: serum sodium concentration.
ΔSNa: serum sodium increase during the first 24 h of correction by hypertonic saline.
OSM_1: serum osmolality in hyponatremia.
OSM_2: serum osmolality 24 h after correction.

In Group I, despite a 10-fold increase in blood urea levels, rats did not present major behaviour changes except a reduction in spontaneous motor activity.

As shown in Table 1, 24 h after NaCl injection, rats were corrected largely above the toxic threshold for brain (mean ΔSNa 32 ± 5 mEq/l/24 h).

During the subsequent days, only one rat developed typical neurologic signs and symptoms of brain myelinolysis with ataxic gait, hyperexcitability with the rat jumping all over the cage and hitting against the walls, either spontaneously or after stimulation [17,28]. This rat presented a correction level of ΔSNa 32 mEq/l (day 5) with concomitant blood urea level of 84 mmol/l and was found dead on day 3 after correction.

Two other rats were found dead in their cages (day 3 and day 4 after NaCl administration) without previous development of neurologic dysfunction. Dead could be potentially attributed to further deterioration of renal function and major azotemia in these two animals. Twelve of the 15 rats (80%) in this Group I survived up to day 10. All of them fared well, remained asymptomatic and regained weight.

Brain analysis of these 12 surviving rats of Group I demonstrated normal histologic features in all of them. No myelinolytic lesions could be observed in these animals (see Fig. 1).

By contrast, *in controls 1 and 2*, despite similar levels of correction (ΔSNa 29 mEq/l/24 h) all the rats (9/9 in control 1 and 15/15 in control 2, $p < 0.001$ compared to Group I, see Table 1) presented severe neurological impairment, exhibiting signs and symptoms typically encountered in myelinolysis (hyperactivity and hyperirritability, spasticity of the extremities, paralysis of the limbs, occasional seizure activity) [17,28].

The outcome was catastrophic in these controls, as only one rat survived up to day 10 in control 1 (no significant azotemia despite $HgCl_2$ injection; survival 1/9, $p < 0.001$ compared to Group I) or in control 2 (no azotemia; survival 4/15, $p < 0.005$ compared to Group I). Brain analysis in the five surviving rats in the control groups showed typical symmetrical demyelinating lesions (area of demyelination with spongy changes, gliovascular proliferation, foamy macrophage infiltration and neuronal loss) located in the cerebellum, thalamus, basal ganglia, tegmentum [17,28].

The slight increase in urea in control 1 (11 ± 5 mmol/l) does not provide any protective effect against neurological complications in this group.

Plasma osmolality was measured in additional rats in a separated set of experiments for each group on days 4 and 5. These rats are not included in the previous results.

No significant difference could be observed in the different groups between calculated and measured plasma osmolality: in Group I: 288 vs. 290 mosM/kg H_2O on day 4 and 366 vs. 368 mosM/kg H_2O after correction; in control 1: 237 vs. 236 mosM/kg H_2O and 284 vs. 286 mosM/kg H_2O; and in control 2: 228 vs. 229 mosM/kg H_2O and 277 vs. 278 mosM/kg H_2O) (see Table 1).

Thus, we can conclude that tolerance to high correction levels of SNa (≈ 30 mEq/l/24 h) was strikingly improved in animals with azotemic state (survival 12/15 in Group I vs. 5/24 when non-azotemic rats of controls 1 and 2 are pooled, $p < 0.001$) (see Fig. 1).

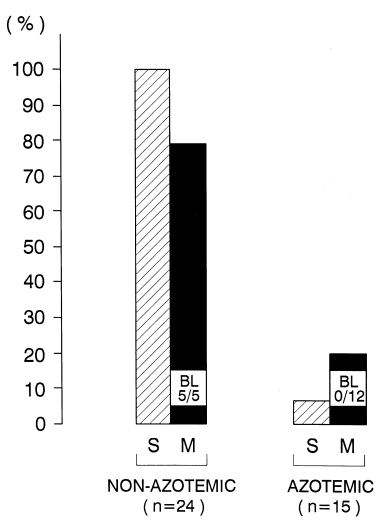

Fig. 1. Neurological outcome in non-azotemic ($n = 15$) and azotemic ($n = 24$) rats. Neurological symptoms after correction (S, square with diagonally stripes) were present in all non-azotemic but in only 6.6% of the azotemic rats ($p < 0.001$). Mortality (M, ■) was also clearly lower in azotemic rats ($p < 0.001$). All the surviving ($n = 5$) non-azotemic rats presents brain lesion (BL) when no rats (0/12) develop myelinolysis in the azotemic group.

4. Discussion

The present study shows in a remarkable way that a given gradient for SNa correction, usually fatal in otherwise normal but hyponatremic rats, was perfectly tolerated when imposed on acute azotemic (48 h) animals.

Our observation is consistent with the clinical observation of only seldom development of myelinolysis in uremic and hyponatremic patients treated with dialysis [23].

In our experiments, renal failure was induced by $HgCl_2$ administration causing reversible proximal tubular necrosis [7,13]. Recovery from renal damage generally occurs after 9–14 days in this model [7]. The end point of our experiments was set at day 10. We demonstrate that chronic hyponatremic rats with superimposed azotemia for at least 48 h preceding the administration of hypertonic saline, were able to tolerate a very large increase in SNa with only very few myelinolysis-related brain damage and/or death (see Table 1 and Fig. 1).

The difference between azotemic rats compared to non-azotemic controls was striking: 80% of the animals with renal failure (Group I) survived after a large gradient of SNa correction (≈ 30 mEq/l/24 h) without neurologic

complications and single brain demyelination (Fig. 1). In just one of the three rats dying before day 10 in Group I, the fatal outcome could be clearly attributed to myelinolysis. In the two other animals, azotemia by itself could have been a potential cause of the death.

Similar levels of SNa correction in hyponatremic rats without azotemia (controls 1 and 2) were responsible for a catastrophic outcome, as largely documented in previous studies [2,17,18,28]. We previously showed also that rats presenting with severe neurologic symptoms before day 10 (as observed in controls 1 and 2), when rescued by secondary SNa lowering, presented in fact typical cerebral damage corresponding to myelinolysis when brain analysis was performed on day 10 [18,20].

The intimate mechanisms underlying our observation remain unknown. However, different hypothesis must be considered.

Growing evidence points to excessive brain dehydration generated by the osmotic stress as causative factor for brain myelinolysis following treatment of hyponatremia. For a given osmotic gradient, chronic (>48 h) hyponatremic brain is more prone to dehydration than normonatremic brain [19,24,27].

Experimental data showed that once brain is fully adapted to hyponatremia, cerebral tissue is depleted in electrolytes (sodium, chloride and potassium), as well as in organic osmolytes (amino acids, polyhydric alcohols, methylamine).

During correction of hyponatremia, the restoration of brain osmolyte content is gradual, taking 24 h for electrolytes and 5–10 days for most organic osmolytes to reaccumulate being required. Obviously, this process could be easily overwhelmed in case of inappropriate (excessive) serum sodium increase [11,12,19,29].

The definite cellular events connecting excessive brain dehydration to myelinolytic injury remain to be elucidated. We know that hypoxia does not seem to play a responsible role [6,21]. Brain rehydration by relowering SNa concentration in the initial hours or days after overcorrection of the SNa could clearly prevent subsequent brain damage in rats [18,20], rendering the implication of hypoxia very unlikely.

In a previous work we could show in rats that correction of chronic hyponatremia with exogenous urea significantly reduced the incidence of myelinolysis [17].

Urea slowly diffuses through the BBB with an equilibration time of 4–10 h [9]. Therefore, urea was used in the past to reduce brain edema. Conversely, when plasma urea concentration decreases, the low rate of urea diffusion creates a brain-to-plasma gradient promoting brain water retention. This ''reverse urea effect'' is one of the mechanisms proposed to explain the brain swelling observed in the post-dialysis ''disequilibrium syndrome'' [14]. In a similar way, the exogenous administration of urea could potentially exert a protecting effect on brain tissue against osmotic injury during the correction of hyponatremia. Indeed, in our previous model, exogenous urea was administered twice daily and urea levels (maximal levels 25–33 mmol/l) decrease during the interval between two injections [17].

Results obtained in the present work in azotemic rats show a better tolerance to the osmotic stress than the one we observed after correcting hyponatremia with exogenous urea. The difference between these two models consists mainly in the relative constancy of plasma urea levels in the azotemic model during the correction phase (see Table 1). Therefore, the ''reverse urea effect'' could not be considered as protection for brain tissue provided by the uremic state in Group I.

Interestingly, Trachtman et al. [26] recently showed in rats that acute azotemia activated the cerebral cell volume regulatory adaptation, allowing the accumulation of brain organic osmolytes. Triggering brain osmolytes recovery could be another mechanism by which urea potentially protects brain against excessive dehydration. This phenomenon, however, is somewhat disputed [15].

Another possibility is the response modification of the BBB to the osmotic stress induced by azotemia during serum sodium correction. Indeed, Adler et al. [1] recently showed that chronic hyponatremia lowers the osmotic threshold for BBB disruption during correction of the SNa. Verbalis et al. [30] demonstrated the presence of activated complement in the brain of rats with myelinolysis, suggesting that influx of complement, known to be toxic for oligodendrocytes, is precipitated by BBB opening and contributes in the pathogenesis of demyelination. Whether azotemia prevents disruption of the BBB and subsequent complement activation in the brain is unknown, but could possibly be another protecting mechanism.

Another explanation could be the counteraction of high urea levels in the brain on the potential deleterious effect of the intra cerebral hyperionisation during the correction of SNa [12,19]. In some species (e.g., sharks), urea and organic osmolytes in definite ratio are used to increase intracellular osmolality under condition of water stress [16].

Finally, various metabolic changes more specifically related to renal failure rather than properties of urea itself could be implicated.

In conclusion, we showed that in chronic hyponatremic rats with concomitant azotemia (48 h) large increase in serum sodium are tolerated without significant damage. The mechanisms by which azotemia strikingly reduces the incidence of brain lesions and death remain to be elucidated. Our observation also provides important informations for the clinician managing patients with renal failure, frequently exposed to serum sodium disturbances [23].

Acknowledgements

This work was supported by a grant from the Fonds National de la Recherche Scientifique (FNRS) (no.

1.5.193.96F and 1.5.198.97). Parts of this study were presented in a preliminary form at the 30th Annual Meeting of the American Society of Nephrology, San Antonio, TX, 1997 and appeared in Abstract form in the J. Am. Soc. Nephrol. 1997; 8: 107A. The authors thank Mrs. Dierick for her technical help and Mrs. C. Piesen for secretarial assistance.

References

[1] S. Adler, J.G. Verbalis, D. Williams, Effect of rapid correction of hyponatremia on the blood-brain-barrier of rats, Brain Res. 679 (1995) 135–143.
[2] J.C. Ayus, R. Krothapalli, D.L. Armstrong, J.H. Norton, Symptomatic hyponatremia in rats: effect of treatment on mortality and brain lesions, Am. J. Physiol. 257 (1989) F18–F22.
[3] G. Decaux, S. Brimioulle, F. Genette, J. Mockel, Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea, Am. J. Med. 69 (1980) 99–106.
[4] G. Decaux, J. Unger, S. Brimioulle, J. Mockel, Hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone: rapid correction with urea, sodium chloride and water restriction therapy, JAMA 247 (1982) 471–474.
[5] G. Decaux, M. Coffernils, S. Brimioulle, B. Hanson, B. Namias, F. Prospert, A. Soupart, In severe acute or chronic hyponatremia treatment with urea is safe for correction of serum sodium of 12–20 mEq/l/24 h, J. Am. Soc. Nephrol. 5 (3) (1994) 366, Abstract.
[6] G. Decaux, L. Crenier, B. Namias, C. Gervy, A. Soupart, Normal acid–base equilibrium in acute hyponatremia and mixed alkalosis in chronic hyponatremia induced by arginine vasopressin or 1-deamino-8-D-arginine vasopressin in rats, J. Lab. Clin. Med. 123 (1994) 892–898.
[7] A. Fujimura, T. Sudoh, K. Dhashi, A. Ebimara, Urinary excretion of furosemide in rats with $HgCl_2$-induced acute renal damage, Life Sci. 51 (1992) 1501–1507.
[8] B.I. Karp, R. Laureno, Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia, Medicine 72 (1993) 359–373.
[9] C.R. Kleeman, H. Dauson, E. Leven, Urea transport in the central nervous system, Am. J. Physiol. 203 (1962) 739–747.
[10] R. Laureno, B. Illowski, Myelinolysis after correction of hyponatremia, Ann. Int. Med. 126 (1997) 57–62.
[11] Y.H. Lien, J.I. Shapiro, L. Chan, Study of brain electrolytes and organic osmolytes during correction of hyponatremia. Implications for the pathogenesis of central pontine myelinolysis, J. Clin. Invest. 88 (1991) 303–309.
[12] Y.H. Lien, Role of organic osmolytes in myelinolysis. A topographic study in rats after rapid correction of hyponatremia, J. Clin. Invest. 95 (1995) 1579–1586.
[13] E.M. McDowell, R.B. Nagle, R.C. Zalme, J.S. McNeil, W. Flamenbaum, B.F. Trump, Studies on the pathophysiology of acute renal failure: I. Correlation of ultrastructure and function in the proximal tubule of the rat following administration of mercuric chloride, Virchows Arch. B: Cell Pathol. 22 (1976) 173–196.
[14] S.M. Silver, J.A. Desimone, D.A. Smith, R.H. Sterns, Dialysis disequilibrium syndrome (DDS) in the rats: role of the ''reverse urea effect'', Kidney Int. 42 (1992) 161–166.
[15] S.M. Silver, R.H. Sterns, M.L. Halperin, Brain swelling after dialysis: old urea or new osmoles?, Am. J. Kidney Dis. 28 (1996) 1–13.
[16] G.N. Somero, Protons, osmolytes, and fitness of internal milieu for protein function, Am. J. Physiol. 251 (1986) R197–R213.
[17] A. Soupart, A. Stenuit, O. Perier, G. Decaux, Limits of brain tolerance to daily increments in serum sodium in chronically hyponatremic rats treated with hypertonic saline or urea: advantage of urea, Clin. Sci. 80 (1991) 77–84.
[18] A. Soupart, R. Penninckx, L. Crenier, A. Stenuit, O. Perier, G. Decaux, Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering, Kidney Int. 45 (1994) 193–200.
[19] A. Soupart, G. Decaux, Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications, Clin. Nephrol. 46 (1996) 149–169.
[20] A. Soupart, R. Penninckx, A. Stenuit, G. Decaux, Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms, J. Neuropathol. Exp. Neurol. 55 (1996) 594–601.
[21] A. Soupart, R. Penninckx, A. Stenuit, G. Decaux, Lack of major hypoxia and significant brain damage in rats despite dramatic hyponatremic encephalopathy, J. Lab. Clin. Med. 130 (1997) 226–231.
[22] A. Soupart, M. Ngassa, G. Decaux, Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia, Clin. Nephrol. 6 (1999) 383–386.
[23] R.H. Sterns, S.M. Silver, Hemodialysis in hyponatremia: is there a risk?, Semin. Dial. Transpl. 3 (1990) 3–4.
[24] R.H. Sterns, D.J. Thomas, R.H. Herndon, Brain dehydration and neurologic deterioration after rapid correction of hyponatremia, Kidney Int. 35 (1989) 69–75.
[25] R.H. Sterns, H. Oocdol, R.W. Schrier, R.G. Narins, Hyponatremia: pathophysiology, diagnosis and therapy, in: Narins, Clinical Disorders of Fluid and Electrolyte Metabolism, McGraw-Hill, New York, 1994, pp. 583–615.
[26] H. Trachtman, S. Futterweit, W. Tonidandel, S.R. Gullans, The role of organic osmolytes in the cerebral cell volume regulatory response to acute and chronic renal failure, J. Am. Soc. Nephrol. 3 (1993) 1913–1919.
[27] J.G. Verbalis, F. Baldwin, A.G. Robinson, Osmotic regulation of plasma vasopressin and oxytocin following sustained hyponatremia, Am. J. Physiol. 250 (1986) R444–R451.
[28] J.G. Verbalis, A.J. Martinez, Neurological and neuropathological sequelae of correction of chronic hyponatremia, Kidney Int. 39 (1991) 1274–1282.
[29] J.G. Verbalis, S.R. Gullans, Rapid correction of hyponatremia produces differential effects on brain osmolyte reaccumulation in rats, Brain Res. 106 (1993) 19–27.
[30] J.G. Verbalis, E.A. Baker, Y. Tian, S. Adler, Immunocytochemical evidence in support of blood-brain-barrier disruption and complement activation in the brain following rapid correction of chronic hyponatremia in rats, J. Am. Soc. Nephrol. 8 (1997) 108A, Abstract.
[31] F. Zarinetchi, T. Berl, Evaluation and management of severe hyponatremia, Adv. Intern. Med. 41 (1996) 251–283.