Urea minimizes brain complications following rapid correction of chronic hyponatremia compared with vasopressin antagonist or hypertonic saline

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Hyponatremia is a common electrolyte disorder that carries significant morbidity and mortality. However, severe chronic hyponatremia should not be corrected rapidly to avoid brain demyelination. Vasopressin receptor antagonists (vaptans) are now being widely used for the treatment of hyponatremia along with other alternatives like hypertonic saline. Previous reports have suggested that, in some cases, urea can also be used to correct hyponatremia. Correction of severe hyponatremia with urea has never been compared to treatment with a vaptan or hypertonic saline with regard to the risk of brain complications in the event of a too rapid rise in serum sodium. Here, we compared the neurological outcome of hyponatremic rats corrected rapidly with urea, lixivaptan, and hypertonic saline. Despite similar increase in serum sodium obtained by the three drugs, treatment with lixivaptan or hypertonic saline resulted in a higher mortality than treatment with urea. Histological analysis showed that treatment with urea resulted in less pathological change of experimental osmotic demyelination than was induced by hypertonic saline or lixivaptan. This included breakdown of the blood–brain barrier, microglial activation, astrocyte demise, and demyelination. Thus, overcorrection of hyponatremia with urea resulted in significantly lower mortality and neurological impairment than the overcorrection caused by lixivaptan or hypertonic saline.

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Osmotic demyelination syndrome (ODS) is the most feared complication during the treatment of hyponatremia. It typically occurs few days after the too rapid correction of hyponatremia and is characterized by evidence of demyelination in the basal ganglia, subcortical areas, and the pons. The clinical signs are variable depending on the demyelinated tracts involved.[1,2] The magnitude of increase of serum sodium (SNa) in 24 h is the most important risk factor of osmotic demyelination, but that increase in SNa depends on many variables and is poorly predictable during hyponatremia correction.[3] The sequence of events leading to demyelination after rapid correction of severe hyponatremia is still not well understood. During chronic hyponatremia, a significant decrease in the content of brain organic osmolyte contributes to the osmotic buffering of the brain to prevent edema; when chronic hyponatremia is corrected rapidly, the re-accumulation of these osmolytes is slow[4,5] and the delay in the reaccumulation of these small molecules might play a part in the events leading to ODS. Recently, we have shown that astrocyte death occurs very early in ODS and is accompanied with a loss of astrocyte–oligodendrocyte gap junctions,[6] which may compromise astrocyte trophic support to oligodendrocyte, integrity of the blood–brain barrier (BBB), and also induce microglial activation. Indeed, the well-defined histological hallmarks of ODS are BBB breakdown, microglial activation, and demyelination. Several vasopressin receptor (V2R) antagonists have been approved for the correction of euvolemic and hypervolemic hyponatremia around the world.[7] These molecules called vaptans act by inhibiting vasopressin-dependent translocation of the water channel at the lumen of the distal circonvoluted tubule and therefore water reabsorption; these events will induce electrolyte-free diuresis and increase the SNa levels. Although in most of the studies with vaptans the reported increment of SNa is <10 mEq/l/24 h, there is a risk of a higher increase in SNa,[8,9] and a recent meta-analysis showed that the risk of an increase of serum sodium of >10 mEq/l/day with vaptans is around 10%.[10] Preliminary animal studies have suggested that vaptans could carry some risk of ODS.[11,12] However, so far only one case of human ODS has been published in which the use of vaptans unfortunately led to an excessive

correction gradient (66 mEq/l over 72 h) along with hyperosmolarity.[13] Another option for the treatment of hyponatremia is urea, and our team has reported that urea is effective in correcting euvolemic and even hypervolemic hyponatremia.[14,15] Interestingly, urea, through an unclear mechanism, acts as a cryoprotectant and an osmoprotectant in amphibians.[16,17] It has also been reported that urea could protect rat heart during electrolysis and increase murine kidney cell viability after hyperosmotic stress.[18,19] Our previous experimental studies suggested that rapid correction of severe hyponatremia with urea might carry a lower risk of neurological complications when compared with treatment with hypertonic saline (HS).[20,21] The protection afforded by treatment with urea seems to be independent of the kinetics of the other major organic osmolyte re-accumulation during hyponatremia correction.[20] It remains, however, unknown whether correction of hyponatremia with urea or vaptans is accompanied by any significant changes on the histological hallmarks of osmotic demyelination such as BBB rupture, microglial activation, and astrocyte loss. We wanted to investigated the effects of overcorrection of hyponatremia with urea, HS, and a V2R antagonist on an experimental model of ODS.

RESULTS

Compared with HS, both urea and lixivaptan are effective in correcting chronic hyponatremia in rats

Administration of a liquid diet with vasopressin infusion resulted in hyponatremia in all the six studied groups of rats (see Supplementary Figure S1 online for experimental design and Table 1 for biochemical parameters). Mean SNa values after the induction of hyponatremia ranged from 108 to 114 mEq/l. In all groups, there was a sharp increase of the SNa 24 h after the initiation of the treatment (32–33 mEq/l), regardless of the experimental paradigm.

Fractionated doses of HS or lixivaptan induced a similar twelfth hour SNa increment compared with urea (16 ± 1, 18 ± 1 and 19 ± 1 mEq/l respectively, Table 1 and Figure 1). Blood level of urea was higher in animals that received urea compared with animals treated with lixivaptan or HS.

Mortality and neurological manifestations associated with overcorrection of hyponatremia are significantly less when urea is used for correction than when lixivaptan or HS was used for correction

At 24 h after the beginning of the correction of hyponatremia, animals treated with lixivaptan or HS started to show neurological manifestations described in experimental ODS (lethargy, seizures, paralysis, and coma or death). Fewer animals treated with urea displayed those signs, which were less marked than in animals treated with V2R antagonist or HS (Figure 2a, $P<0.01$ for neurological score urea vs. lixivaptan or HS). In experiment 1, 6 days after the beginning of the correction of SNa, the mortality in the group of animals treated with urea was only 27 vs. 65 and 76% of animals treated with lixivaptan and HS, respectively ($P=0.017$ by Fischer's exact test—Table 1). Survival curve analyses (Figure 2c) confirmed survival benefit of treatment with urea vs. a bolus of lixivaptan or HS ($P=0.003$ by log-rank test).

The serum sodium increment after the first 12 h does not account for the effect of urea in ODS

Although the magnitude of SNa increase at 24 h is the main determinant of ODS,[1,2,22–25] earlier work has suggested that

Table 1 | Biological parameters of animals in experiments 1 and 2

	After the start of the correction										
	0 h		12 h		24 h		SNa increment		Outcome		
	SNa	Urea	SNa	Urea	SNa	Urea	12 h	24 h	Dead	Alive	Mortality
Experiment 1											
Group 1 $n=23$, lixivaptan once	112 ± 1	23 ± 2	NA	NA	145 ± 1	71 ± 9	NA	33 ± 1	15	8	65%
Group 2 $n=22$, urea 4 doses	108 ± 1	31 ± 1	NA	NA	141 ± 2	143 ± 30	NA	33 ± 1	6	16	27%
Group 3 $n=25$, NaCl single bolus	109 ± 1	28 ± 3	NA	NA	140 ± 1	45 ± 6	NA	31 ± 1	19	6	76%
Experiment 2											
Group 4 $n=17$, lixivaptan 2 doses	112 ± 1	29 ± 3	131 ± 3	42 ± 4	145 ± 2	52 ± 5	19 ± 2	33 ± 2	12	5	71%
Group 5 $n=16$, urea 4 doses	114 ± 1	22 ± 1	133 ± 1	158 ± 30	147 ± 1	187 ± 40	18 ± 1	32 ± 1	4	12	25%
Group 6 $n=15$, NaCl 2 doses	112 ± 2	27 ± 1	128 ± 1	27 ± 2	145 ± 2	44 ± 3	16 ± 1	32 ± 1	14	1[a]	93%

Abbreviations: NA, not applicable; SNa, serum sodium.
In the first experimental paradigm (Experiment 1), lixivaptan or hypertonic saline was administered in a single intraperitoneal (ip) bolus and urea in four divided doses. SNa was measured before the correction (0 h) and 24 h after the beginning of the correction. Groups 1–3 had similar increases in their Na at 24 h. ($P<0.001$ for SNa before and after in all the groups by paired *t*-test and $P=$ NS for increment in Na between all the groups by analysis of variance (ANOVA) test.)
In the second experimental paradigm (Experiment 2), lixivaptan or hypertonic saline was administered ip in two doses 12 h apart and urea ip in four doses every 6 h with Na measured at 0, 12, and 24 h. The three treatments induce a similar increment in Na at 12 and 24 h ($P=$ NS between the three groups by ANOVA both at 12 and 24 h).
In experiments 1 and 2, animals receiving urea had a lower mortality than animals receiving lixivaptan ($P=0.017$ and 0.015, respectively, by Fischer's exact test) or hypertonic saline ($P=0.0012$ and 0.0002, respectively). No difference in mortality was found in animals receiving lixivaptan vs. hypertonic saline in both experiments ($P=0.529$ and 0.178, respectively).
SNa = serum sodium in mmol/l and urea in mg/dl (to convert to blood urea nitrogen, multiply by 0.357). Range for urea groups 2 and 5 at 24 h: 68–620 and 79–590 mg/dl, respectively.
[a]The animal was alive early on day 10 and died later on the same day.