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Original Article

Mild water restriction with or without urea for the longterm treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH): Can urine osmolality help the choice?

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ABSTRACT

Background: Treatment options for chronic SIADH include water restriction (WR) and urea. The usefulness of urine osmolality to guide the choice of the treatment option is not clearly defined. We hypothesized that urine osmolality can indicate whether treatment with mild water restriction alone could be successful.
Methods: Retrospective Review of clinical and biochemical (blood and urine) data of patients with chronic SIADH treated for at least one year with mild WR (1.5–2 l/day) either with or without urea.
Results: Twenty nine patients were included. Nine patients were treated by mild WR. Mean serum sodium (SNa) and mean Uosm were 129 ± 2 mEq/l and 274 ± 78 mOsm/kgH2O respectively before WR, and increased to 138.5 ± 3 mEq/l and 505 ± 87 mOsm/kgH_2O ($P < 0.001$). Eight patients were treated with mild WR and 15 g urea daily, the SNa and Uosm before treatment were 127.5 ± 3 mEq/l and 340 ± 100 mOsm/kgH_2O respectively and increased to 136.5 ± 1 mEq/l and 490 ± 151 mOsm/kgH_2O ($P < 0.001$). Four of the eight patients had a permanent low solute intake which contributed to hyponatremia. Twelve patients needed 30 g urea daily combined with mild WR. The SNa and Uosm were respectively 126 ± 2 mEq/l and 595 ± 176 mOsm/kgH_2O and increased to 136.5 ± 2 mEq/l and 698 ± 157 mOsm/kgH_2O ($P < 0.05$). Uosm increased in most of the treated patients.
Conclusions: About 30% of patients could be treated by moderate WR alone. All these patients presented an initial urine osmolality lower than 400 mOsm/kgH_2O.

1. Introduction

Hyponatremia is the most frequent electrolyte abnormality observed in clinical practice. Even mild to moderate hyponatremia (130–135 mEq/l), has been associated with gait instability, attention deficit, falls, bone fractures, osteoporosis, and results in an increased mortality both in the inpatient and the outpatient setting [1–3]. However, so far no study has shown that the treatment of asymptomatic hyponatremia could reverse the increased mortality or morbidity associated with low serum sodium levels [4].

In the elderly, the chronic syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the leading causes of hyponatremia [2]. Treatment options for chronic SIADH include water restriction, loop diuretics (usually combined with oral salt intake), urea, or V2 antagonists (vaptans) [4–7]. Long term adherence to water restriction of less than 800 ml/day is usually hard to achieve [6] presumably because it highly interferes with the patient's quality of life and, because this treatment option might carry the risk of binge water intake and ensuing water intoxication.

We wanted to determine if the initial urine osmolality could help to distinguish between patients that could benefit from an acceptable mild WR (≤1500–2000 ml/day) and those who will need a combination of WR and urea.

2. Patients and methods

We retrospectively reviewed the records of patients with chronic SIADH that were treated in our unit from 2011 to 2016.

To establish the diagnosis of SIADH, we used the classical criteria mentioned in the European Guidelines: (i) clinical euvolemia, (ii) urine osmolality >100 mosm/l, (iii) urine sodium concentration >30 mmol/l (with normal dietary intake), (iiii) lack of renal, pituitary, thyroid and adrenal insufficiency, (iiiii) no recent use of diuretics [4]. Past medical, social and medical history, was extracted from the records. Patients that were included in previous studies were excluded [8].

Patients with other causes of hyponatremia (based on endocrine function test results, medication history) were excluded and among patients with chronic SIADH, we included only those with: (i) a

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duration of treatment of more than one year, (ii) hyponatremia lasting at least 4 months before the initiation of treatment, (iii) an initial SNa ≤ 132 mmol/l. Patients with cancer and patients with a history of polydipsia (arbitrary defined by a water or beer intake higher than 4 l/day) were also excluded [9]. When classical causes of SIADH were excluded (on the basis of brain and chest CT, lack of endocrine deficit, and review of the intake of drugs known to induce hyponatremia) a diagnosis of idiopathic SIADH was made [2].

Water restriction (WR) was defined as a water intake lower than 1500–2000 ml/day. We performed a comprehensive assessment of fluid intake which included all liquid intake such as soup and yoghurt. Fruits and vegetables were not taken into account.

During the treatment period the patients were seen usually every 3 to 4 months with usual blood chemistry. Urine osmolality just before WR or urea therapy are reported in the tables as well as the last urine osmolality measured at the same time as that of SNa.

Changes in body weight and acid-base data were not recorded. We also recorded the dose of urea used in patients taking urea (either crystalline urea or effervescent urea) [10,11].

Statistical analysis was performed with Graphpad software version. Kolmogorov and Smirnov test was first applied to determine if the analyzed variables were distributed normally. Comparisons between means were performed with student *t*-test or paired student *t*-test when appropriate. A p value of <0.05 was considered statistically significant. Data are presented as mean ± SD.

This study was approved by the ethics committee of hospital Erasme (Université Libre de Bruxelles).

3. Results

Twenty nine patients met the inclusion and had none of the exclusion criteria.

None of the studied patients had hypokaliemia.

All the patients who did not normalize their SNa after a few days of WR (usually 3 to 4 days) were treated with urea. Some patients were treated first by 15 g/day and this dose was increased to 30 g/day if SNa was not normalized (≥135 mmol/l). In some other patients the initial dose was 30 g and was decreased to 15 g/day if SNa rose aboveg ≥142 mmol/l. Of note, six patients presented falls and 2 patients had a bone fracture before treatment initiation. Upon treatment initiation, no patient experienced recurrence of a fall.

Interestingly, during the follow-up of all these patients, about 20% of SNa measurements performed under treatment still revealed mild episodes of hyponatremia (lowest value 132 mmol/l).

In all patients SNa and urine osmolality were relatively stable before treatment was initiated. The low value observed in some patients (<300 mOsm/kg) was not transient and was observed repeatedly in several measurements. Probably, this did not reflect escape to ADH-induced antidiuresis but rather a less severe impairment of diluting ability [9].

Based on their response to moderate water restriction, patients were divided in 3 groups.

Group I included all patients who responded to mild water restriction only, requiring no additional urea. Group II was composed of patient that required 15 g of urea on top of water restriction and group III included patient that required 30 g of urea along with water restriction.

Group I consisted of 9 patients. Twenty patients did not normalize their serum sodium after moderate water restriction. Among those, eight patients were successfully treated with the addition of 15 g of urea (Group II) and twelve patients normalized their serum sodium after adding 30 g of urea to water restriction (Group III). The data from all three groups are presented in Tables 1, 2 and 3.

All patients in Group I presented with idiopathic SIADH [2,9]. They were all well-nourished and none had psychiatric disorder. These patients had an estimated daily water consumption of around 2.5 to 3.5 l a day before WR was initiated and the water intake consisted of non alchoholic beverage. In all the patients, normalization of SNa was associated with an increase in urine osmolality (from 274 ± 78 to 505 ± 87 mOsm/kg H_2O; $P < 0.001$). Mean initial urine osmolality in this group was significantly lower than the two groups treated with urea (mean value 481 ± 175; $P < 0.001$; for $n = 20$).

In group II, ($n = 8$ - Table 2), despite mild water restriction hyponatremia was not corrected. Intake of 15 g of urea (representing 250 mmol) significantly increased SNa. Mean urine osmolality increased from 340 ± 100 to 490 ± 150 mOsm/kg H_2O ($P < 0.001$). Four patients presented a low BMI (<18 kg/m^2) and a low urine osmolality (from 132 to 250 mOsm/kg). Food intake in all these 4 patients (Nr 10–13 in Table 2) was very low without obvious reasons except in one patient who presented dysphagia since cervical radiotherapy for mouth cancer. Three patients presented idiopathic SIADH.

Due to gustative intolerance to the usual solution of urea, two of these patients received the more tasteful effervescent formulation of urea (combined with NaHCO3, sucrose and citric acid) with excellent adherence [4].

Patient from group III ($n = 12$ - Table 3) were treated with 30 g urea daily (representing 500 mmol and mild WR). Urine osmolality increased in most patients during treatment.

One patient (Nr. 23) needed 30 g urea daily despite low urine osmolality (200 mOsm/kg H_2O) likely because mild WR was not well respected. The great variability in serum urea observed in the urea-treated participants is related to the difference in the time of urea intake between them. The majority of patients in this last group presented with evidence of brain pathology (brain hematoma, brain tumors …).

Table 1
Pertinent blood and urine parameters in 9 patients with SIADH treated by mild water restriction (1.5–2 l/day) during more than one year.

Patient	Before water restriction					During water restriction			Etiology	Co-morbidity
	Age/sex	Fall	SNa (mEq/l)	Urea/Cr (mg/dl)	Uosm/UNa (mOsm/kg H_2O)/mEq/l	SNa (mEq/l)	Urea (mg/dl)	Uosm/UNa (mOsm/kg H_2O)/mEq/l		
1	75/♂	+	131	29/1.0	208/35	137	37	508/60	I	Peripheral artery disease
2	62/♀	−	127	17/0.9	141/38	140	26	537/70	I	bronchiectasias
3	80/♀	−	131	31/0.9	269/49	137	40	453/58	I	Polyarthrosis
4	57/♀	−	128	27/1.0	216/41	139	24	544/72	I	Lumbar spinal stenosis
5	60/♀	−	128	20/0.9	395/60	137	39	665/45	I	Arterial hypertension
6	67/♂	−	126	26/0.8	321/35	144	40	510/40	I	Alcoholism
7	86/♀	+	130	43/1.1	325/52	140	30	494/81	I	Polyarthrosis
8	69/♂	−	132	26/0.9	223/36	134	31	330/41	I	Peripheral artery disease
9	64/♀	−	132	20/0.8	375/58	134	22	422/48	I	Obesity
Mean ± SD			129 ± 2	26 ± 7/0.9 ± 0.1	274 ± 78/44 ± 10	138 ± 3*	33 ± 6**	505 ± 87*/47 ± 14		

Uosm = Urine Osmolality (mOsm/kg H_2O); Cr = Creatinine.
UNa = Urine Sodium (mEq/l); I = Idiopathic; SD = standard deviation.
* $P < 0.001$.
** $P < 0.05$.

Table 2
Pertinent blood and urine parameters in 8 patients with SIADH treated by 15 g urea daily and mild water restriction (1.5–2 l/day) during more than one year.

Patient	Before urea administration					During urea administration			Etiology	Co-morbidity
	Age/sex	Fall	SNa (mEq/l)	Urea/Cr (mg/dl)	Uosm/UNa (mOsm/kg H_2O/mEq/l)	SNa (mEq/l)	Urea (mg/dl)	Uosm/UNa (mOsm/kg H_2O)/mEq/l		
10	72/♂	+/BF	127	23/0.6	250/36	136	60	360/33	COPD/LSI	Alcoholism
11	65/♂	−	132	16/0.9	190/32	138	31	229/25	OC/LSI	Peripheral artery disease
12	84/♀	−	121	28/1.0	240/38	136	47	620/40	I/LSI	Polyarthrosis
13	41/♀	−	124	15/0.8	132/30	136	28	250/35	I/LSI	
14	78/♀	−	132	29/1.0	459/50	138	40	550/42	Bronchiectasia	Polyarthrosis
15	64/♀	−	128	8/0.7	430/42	136	12	670/50	I	HTA
16	65/♀	−	125	25/1.1	395/70	136	39	510/55	I	Polyarthrosis
17	85/♂	−	131	33/1.0	388/66	139	24	563/74	I	Diabetes
Mean ± SD			127.5 ± 3.0	22 ± 7/0.8 ± 0.2	340 ± 100/45 ± 15	136 ± 1*	38 ± 14*	490 ± 151*/44 ± 15		

Uosm = Urine Osmolality (mOsm/kg H_2O); BF = bone fracture; LSI = Low Solute Intake; OC = Oral Cancer; Cr = Creatinine.
UNa = Urine Sodium (mEq/l); I = Idiopathic; SD = standard deviation.
* $P < 0.001$.

In all patients urea was well tolerated in the long-term and no case of hypernatremia was observed.

4. Discussion

Our data show that mild water restriction (<1.5–2 l/day) could be effective in about 30% of our patients with chronic SIADH in the long term. We showed that patient that will be more likely to respond to water restriction exhibit a lower urine osmolality (<400 mOsm/kg H_2O; mean value 274 mOsm/kg H_2O) and normal food intake which presumably reflects normal solute intake.

Previous reports have suggested that some patients might be able to follow a strict and severe water restriction (<800 ml/day) particularly in NSIAD [12,13]. However, such levels of water restriction are usually hard to achieve in most patients in the long term [6]. For a daily osmotic load of around 600–900 mOsm and if one assumes a fixed urine osmolality of 400 mOsm/Kg H_2O, the expected urine output is around 1.5 to 2.25 L daily. Thus, to avoid dehydration in the setting of water restriction antidiuretic hormone must be secreted and the urine osmolality will increase. We observed that the urine osmolality increased in our patients and none developed hypernatremia. This suggests that they were in a state of antidiuresis and also that the water restriction was followed by the patients [16] (Fig. 1).

It could be argued that hyponatremia initially developed because the intake of water overwhelmed the diluting capacity of the kidney and that the serum sodium normalized after the intake was adjusted to match the diluting kidney capacity.

We also observed in most of our patients, as previously shown in SIADH, that water restriction increased the levels of the blood urea [14,15]. (Table 1). In group I, one patient presented – before water restriction - a slightly increased urea concentration (♀ 86 – urea 43 mg/dl). We have shown a more important decrease in urea clearance with age than the decrease observed for creatinine clearance [15]. In this study, young patients with SIADH presented lower mean plasma urea (18 ± 8 mg/dl) and higher mean FE urea (58 ± 14%), compared with old patients with SIADH (mean plasma urea 29 ± 8 mg/dl; mean FE urea 44 ± 15%).

All the patient that had normalization of hyponatremia upon mild water restriction presented with idiopathic SIADH which was found to be the main cause of hyponatremia in large series of patients of more than 65 year of age [2,3].

Two-third of patients needed, to normalize SNa, a combination of mild WR with an increase in daily solute intake consisting in 15 or 30 g urea (which represents a solute load of 250 or 500 mmol) (Fig. 1).

The last group of patients received 30 g urea daily (Table 3) in one or two doses. Their initial urine osmolality was around 600 mOsm/kg H_2O.

It is possible that urine osmolality also increased during urea therapy in patients from group II and III likely to avoid dehydration and hypernatremia.

Table 3
Pertinent blood and urine parameters in 12 patients with SIADH treated by 30 g urea daily and mild water restriction (1.5–2 l/day) during more than one year.

Patient	Before urea administration					During urea administration			Etiology	Co-morbidity
	Age/sex	Fall	SNa (mEq/l)	Urea/Cr (mg/dl)	Uosm/Una (mOsm/kg H_2O/mEq/l)	SNa (mEq/l)	Urea (mg/dl)	Uosm/Una (mOsm/kg H_2O/mEq/l)		
18	78/♂	−	125	30/0.8	735/70	133	54	738/60	I	Cardiomyopathy(Δ)
19	63/♀	−	124	27/1.0	675/66	136	44	840/50	I	arterial hypertension
20	82/♀	+/BF	130	21/0.6	350/40	135	47	806/48	I	Polyarthrosis/Diabetes
21	65/♀	−	128	24/0.7	570/85	134	42	669/108	Subdural hematoma	
22	87/♂	−	128	20/0.9	626/72	136	46	650/55	Alzheimer	Diabetes
23	73/♀	+	129	9/0.6	200/31	136	72	325/50	VCI	arterial hypertension
24	76/♂	−	127	25/0.9	650/48	140	40	805/90	VCI	arterial hypertension
25	40/♀	−	129	20/0.8	905/110	140	30	795/95	Glioma	
26	63/♂	+	122	17/1.0	750/140	137	42	530/80	Brain hematoma	Alcoholism
27	54/♀	−	123	13/0.9	580/70	138	45	856/63	Post traumatic brain injury	
28	24/♀	−	130	15/0.8	577/127	136	28	700/100	Glioma	
29	79/♀	−	124	26/0.8	527/144	137	64	661/105	I	Polyarthrosis
Mean ± SD			126 ± 2	21 ± 7/0.8 ± 0.1	595 ± 176/83 ± 38	136 ± 2*	46 ± 12*	698 ± 157**/75 ± 23		

Uosm = Urine Osmolality (mOsm/kg H_2O); UNa = Urine Sodium (mEq/l); BF = bone fracture; I = Idiopathic; VCI = Vascular Cognitive Impairment; (Δ)Ischemic cardiomyopathy without cardiac failure; Cr = Creatinine; SD = standard deviation.
* $P < 0.001$.
** $P < 0.05$.

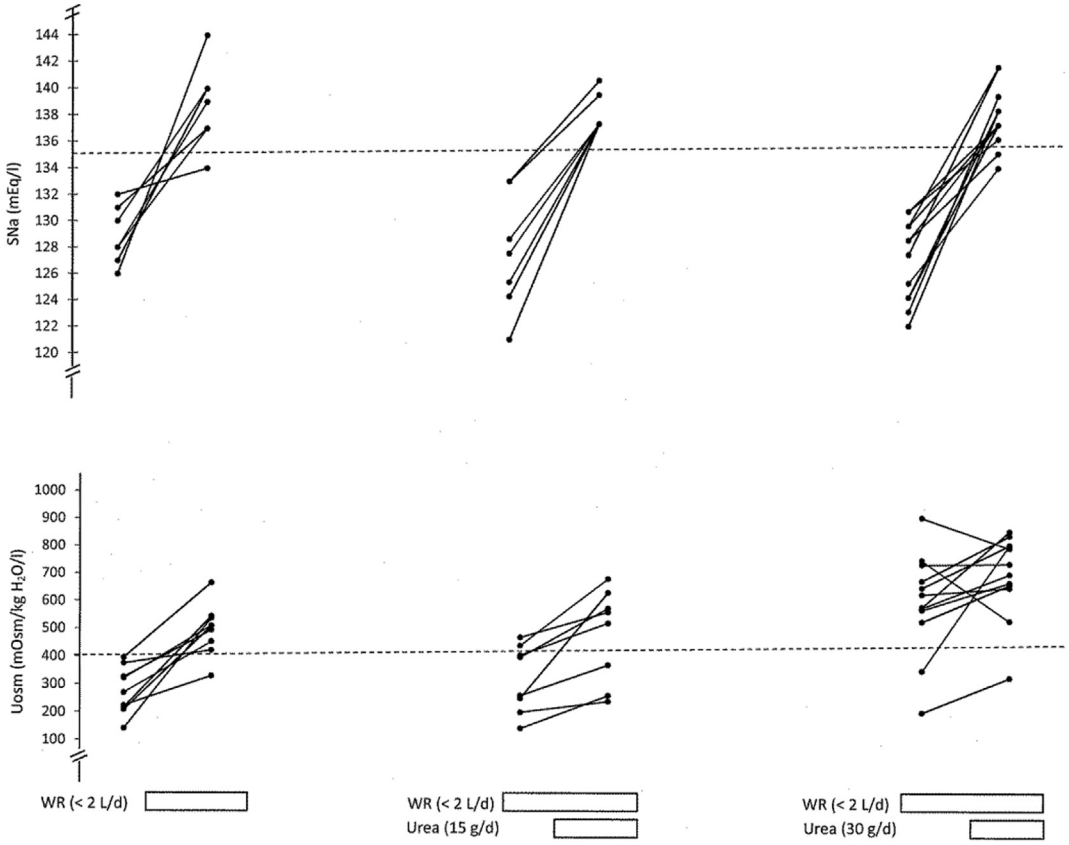

Fig. 1. Evolution of SNa and urine osmolality in 29 patients with chronic SIADH before and during more than one year treatment by simply mild water restriction (WR) (1.5–2 l/day) with or without urea (15 or 30 g/day).

Six patients reported at least one episode of fall and 2 patients had a bone fracture [9] before water restriction or urea therapy. There was no recurrence of falls or fracture after correction of serum sodium. There are no data suggesting that the treatment of mild to moderate hyponatremia results in a decrease in mortality or morbidity (less falls, less bone fractures, recovery of osteoporosis) [3,4] although some studies have suggested that correcting hyponatremia might be beneficial with regards to the length of hospital stay [17].

Urea has been used to treat a wide variety of condition including gastritis or gastric ulcer (even during bleeding episodes), liver metastases, prophylactic treatment of sickle cell disease, Meniere disease, hematuria related to drepanocytosis and widely to treat brain edema and glaucoma [10,11,18].

Urea readily penetrates within the intracellular space and does not usually result in an osmotic gradient. Urea is also rapidly excreted in the urine. This additional load of solute will increase the urine flow rate and urine output which will result in a negative water balance. Those effects support the use of urea to correct hyponatremia. It is possible that the increase in the plasma osmolality brought by urea will trigger ADH secretion and allows to avoid an excessive water loss, dehydration and hypernatremia.

Urea also penetrates into the central nervous system (CNS) slower than into muscle allowing some level of transient intravascular to CNS urea gradient (in 4 to 10 h), This property is beneficial when one need to decrease brain water content and to treat brain edema associated with hyponatremia [18,19].

Some patients could experience mild episodic headache after treatment with 30 g of urea. These headaches are easily prevented when urea is given in two divided doses.

Apart from patients with nasogastric tube like ICU patients [20], the most important drawback of urea is certainly its taste, which could be improved by diluting urea powder in fruit syrup or orange juice. Of note, there is a recently developed less distasteful formulation of urea called “Brussels champagne” [21] (urea 15 g (or 10 g) with sodium bicarbonate 2 g, citric acid 1.5 g and sucrose 200 mg), given in two patients in group 2. It is likely that the addition of 24 mEq Na/day represented only a minor contribution - if any - in reaching normonatremia in our non-Na depleted patients.

All our patients presented hyponatremia for many months and none of them had acute brain injury. In addition, all these patients did not present reduced extra-cellular fluid volume, so that the diagnosis of cerebral salt wasting syndrome (CSW) was unlikely [22].

There are now some international company marketing urea in Europe (Urea NP®, Nutricia Medica, Spain), — 15 or 30 g of urea mixed with citric acid and flavorings - and in the US (Ure—Na™ by Nephcentric). Urea is viewed by the FDA as a medical food supplement (GRAS category: General Regarded As Safe) and therefore does not require a medical prescription (personal communication of Helbert Rondon-Berrios) [23].

The cost of these preparations is highly different from a vaptan [24]. In Belgium, vaptans are not reimbursed for treatments of SIADH (contrary to the reimbursement of polycystic kidney disease) while the cost for the patient of 30 g urea daily during one month is around 5 euros (roughly 5 dollars). Previous studies have shown similar result in patients with SIADH treated with vaptan or urea in the long term [8]. It must be noted that the increase in diuresis with urea therapy is a slow process which occur in 24 h, it is not brisk like with loop diuretics or vaptans [5,25] and more importantly, urea has recently shown a protective effect against brain damage related to too rapid correction of hyponatremia [26–28].

There are some limitations to this study. First its retrospective nature could have impacted data collection although for almost all patient blood and urine parameters were available before and after the treatment was started. It is possible that the water intake either before or

after water restriction began could have been inadequately assessed. The second limitation is due to the small number of patients analyzed, the heterogenicity of the groups and the numerous comorbidities. However it should be pointed that this is the only long term (more than 1 year) follow up study on treatment of chronic SIADH with either mild WR combined or not with urea.

In summary this study supported the hypothesis that urine osmolality is an accurate parameter to predict the response to mild water restriction, acceptable in the long-term. On the other hand, patients with low solute intake and high urine osmolality will be more likely to benefit from a small dose of urea.

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