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Treatment of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone with Urea in Critically Ill Patients

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Key Words
Hyponatremia · Urea · Sodium · Critically ill patients · Syndrome of inappropriate antidiuretic hormone secretion

Abstract
Background: Hyponatremia occurring as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common and potentially lethal complication in critically ill patients. Urea, by inducing renal water excretion and promoting sodium (Na) retention, has been well described as a treatment for chronic SIADH. However, there are limited data on its use for the treatment of SIADH as encountered in patients admitted to the intensive care unit (ICU). We assessed the effects of urea administration for treatment of SIADH in ICU patients. ***Methods:*** Data from ICU patients treated with urea for SIADH between January 2000 and August 2010 were reviewed. The time courses of Na and urea concentrations were analyzed by variance analysis (ANOVA). ***Results:*** Records from 24 patients were analyzed. The most common etiology of SIADH was neurological (18 patients). Before urea administration, the mean serum Na concentration was 124.8 ± 5.9 mEq/l. There was a significant increase in serum Na from the second day of treatment (131.4 ± 3.5 mEq/l, $p < 0.001$) and a normalization of mean serum Na by the fourth day (136.2 ± 4.1 mEq/l, $p < 0.001$). The mean serum urea concentration also increased (from 29.8 ± 11.1 mg/dl before urea to 57.6 ± 24.0 mg/dl on the first day of treatment, $p < 0.001$). ***Conclusions:*** Urea administration appears useful for the treatment of SIADH-associated hyponatremia in critically ill patients. Prospective randomized controlled studies are needed to confirm these results.

Introduction

Dysnatremia, and especially hyponatremia, which is generally defined as a plasma sodium (Na) level <136 mEq/l [1], is a common electrolyte disorder in intensive care unit (ICU) patients [2, 3]. The ionic derangement is associated with increased morbidity and mortality [3–6]. In hypotonic hyponatremia, the excess total body water relative to total body Na content creates an osmotic gradient between the extra- and intracellular compartments, resulting in a shift of water. Depending on the rapidity of onset and the degree of severity, the resultant brain edema can be associated with symptoms ranging from subtle signs to severe neurological impairment (coma, cerebral herniation and death) [7, 8].

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The classification of hypotonic hyponatremia is based on the extracellular fluid volume status of the patient (hypovolemic, euvolemic and hypervolemic hyponatremia). In ICU patients, hyponatremia is frequently the result of specific etiologies, such as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), with slightly high or normal volemia, or the cerebral salt-wasting syndrome – or the more appropriate term, renal salt-wasting syndrome (RSWS) – with hypovolemia [9, 10]. Many factors can lead to SIADH in critically ill patients, including drugs, pulmonary diseases, cancers, but also pain, general anesthesia, nausea and stress [11]. Disorders of the central nervous system can also cause SIADH, so it is commonly encountered in neurocritical care.

Over the last few decades, many treatments have been proposed for the treatment of SIADH, including fluid restriction, which is difficult to use in ICU patients who often require infusions of fluid for additional treatments like antibiotics, lithium, demeclocycline, and hypertonic saline solutions. More recently, vasopressin-receptor antagonists, such as conivaptan, have been reported, in small studies, to be effective in ICU patients [12]. Nevertheless, the routine use of these agents needs further study in terms of their cost and safety profile. Administration of oral urea, by inducing renal water excretion [13] and promoting Na retention, has been well documented in patients with chronic SIADH [14, 15]. Only one study has evaluated urea for the treatment of the SIADH encountered in ICU patients, despite a strong theoretical basis for its usage [16]. We, therefore, reviewed the effects of urea used to correct hyponatremia in patients with SIADH in our ICU.

Methods

After approval by the CHU Charleroi ethical committee, data from all patients admitted to our closed medico-surgical 36-bed ICU who received urea between January 2000 and August 2010 were collected retrospectively from the database of the hospital pharmacy.

Diagnosis of SIADH was established on the basis of the following criteria: clinically euvolemic patient, serum Na concentration <135 mEq/l, urine Na concentration >20 mEq/l, serum osmolality <280 mosm/kg, urine osmolality >200 mosm/kg H_2O (if available), normal renal, thyroid and adrenocortical functions. If the serum osmolality measurement was missing, serum osmolality was estimated using the formula (2× Na concentration + glycemia + urea concentration) (all in mmol/l) [17]. In either case, a measured or calculated serum osmolality <280 mosm/kg H_2O was required for diagnosis of SIADH-associated hyponatremia [18].

The data collected included patient demographics (age, sex, ICU admission diagnosis, length of ICU stay, Acute Physiology and Chronic Health Evaluation II (APACHE II) score [19], Glasgow coma score at the time of diagnosis of hyponatremia, presence of intracranial pressure monitoring, etiology of SIADH). SIADH was classified as due to neurological causes or other (non-neurological) causes because of a possible impact of the etiology on the time course of serum Na concentration. Biological data included urine and plasma concentrations of Na, potassium, blood glucose, urea, creatinine, uric acid, and osmolality from the first day of hyponatremia. Serum Na and urea concentrations were measured each day during urea therapy. We considered SIADH as having resolved when the serum Na concentration was ≥135 mEq/l. Finally, we collected duration of hyponatremia before initiating urea, dose of urea given, duration of the treatment, and any adverse effects noted by the physician as being the result of the urea treatment.

Table 1. Demographic characteristics of the patients

Variable	Mean	SD
Age, years	56	18
Male, %	67	
APACHE II score	17	7
Glasgow coma scale score[1]	11	4
Mortality, %	4	
Length of ICU stay, days	20	13

[1] At the time of diagnosis of SIADH.

Treatment of hyponatremia was protocoled in our ICU and includes hydric restriction with initial isotonic saline (max. 1 liter/day) and administration of urea packaged in 15-gram bags. Urea was administered orally or by nasogastric tube at a median dose of 45 g/day.

To investigate the possible relationship between the dose of urea administered and the severity of hyponatremia, we divided our population according to the median value of the serum Na concentration just before onset of urea therapy (< or ≥127 mEq/l).

Statistical Analysis

Data are expressed as mean ± SD, or median and interquartile ranges (25–75%) as indicated. The time course of serum Na and urea concentrations was analyzed by variance analysis (ANOVA). Correlation was assessed by the Spearman test. Results were considered as significant when $p < 0.05$ was obtained.

Results

During the study period, 42 patients received urea for hyponatremia during their ICU stay. We excluded 18 patients (9 with missing data and 9 who were misdiagnosed as having SIADH) (fig. 1). The demographic characteristics of the 24 remaining patients are reported in table 1. Of these 24 patients, 2 were admitted to the ICU for neu-

Table 2. Biological characteristics of the patients before urea administration

Variable	Value	Number of patients (/24)
Mean serum Na, mEq/l	124.8 ± 5.9	24
Mean urine Na concentration, mEq/l	121.4 ± 47.8	24
Mean measured serum osmolality, mosm/kg	267 ± 24	7
Mean calculated serum osmolality, mosm/kg	259 ± 15	24
Mean measured urine osmolality, mosm/kg	537 ± 159	20
Mean serum urea concentration, mg/dl	29.8 ± 11.1	24
Mean serum creatinine concentration, mg/dl	0.57 ± 0.18	24
Mean serum glucose concentration, mg/dl	160 ± 43	24
Mean serum potassium concentration, mEq/l	4.2 ± 0.3	24

rological symptoms related to hyponatremia (confusion, convulsions); the other 22 patients developed acute hyponatremia during their ICU stay. Etiology of SIADH was neurological in most of the cases [18 patients, including head trauma (n = 12), cerebrovascular accident (n = 4), acute meningitis (n = 1) and subarachnoid hemorrhage (n = 1)]. Non-neurological causes were mainly pneumonia (n = 5). The etiology remained unidentified in 1 case. No patients were receiving diuretics or mannitol at the time of diagnosis.

Biological data before urea administration are shown in table 2. All the data were compatible with SIADH. The delay between diagnosis and administration of urea varied widely, with a median value of 2 (range 0–17) days. Urea was administered for a median duration of 3 (3–6) days. There were no differences in the mean urea dose administered in patients with severe hyponatremia (mean serum Na <127 mEq/l) and in patients with mild hyponatremia (mean serum Na ≥127 mEq/l).

Before urea administration, the mean serum Na was 124.8 ± 5.9 mEq/l. The depth of hyponatremia varied between the patients from 99.7 to 131.0 mEq/l. The time course of Na concentrations for all patients is shown in figure 2a. Natremia increased rapidly with urea therapy, independently of the etiology of the SIADH. There was a significant increase in the mean serum Na concentration of the 24 patients from the second day of treatment (131.4 ± 3.5 mEq/l, $p < 0.001$) with normalization of the mean serum Na level by the fourth day (136.2 ± 4.1 mEq/l, $p < 0.001$) (fig. 2a).

The time course of serum Na concentration during urea therapy in the 18 neurological patients is shown in figure 2b. We also observed a significant increase in the mean serum Na concentration of these 18 patients from the second day of treatment (131.7 ± 3.9 mEq/l, $p < 0.001$). On the fourth day of urea therapy, the mean serum Na concentration was 136.1 ± 3.5 mEq/l ($p < 0.001$) in this population.

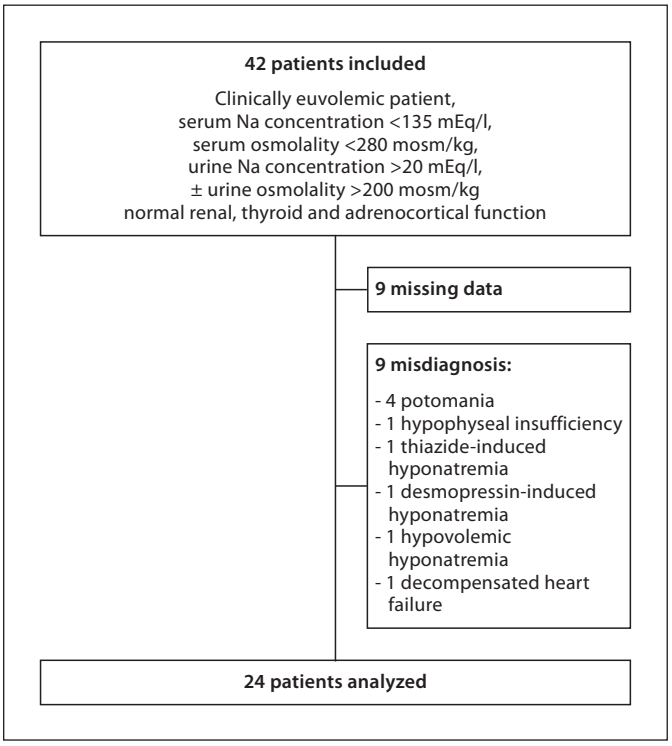

Fig. 1. Flow chart showing the 42 patients who received urea for hyponatremia during their ICU stay. Eighteen patients, 9 with missing data and 9 misdiagnosed as having SIADH, were excluded.

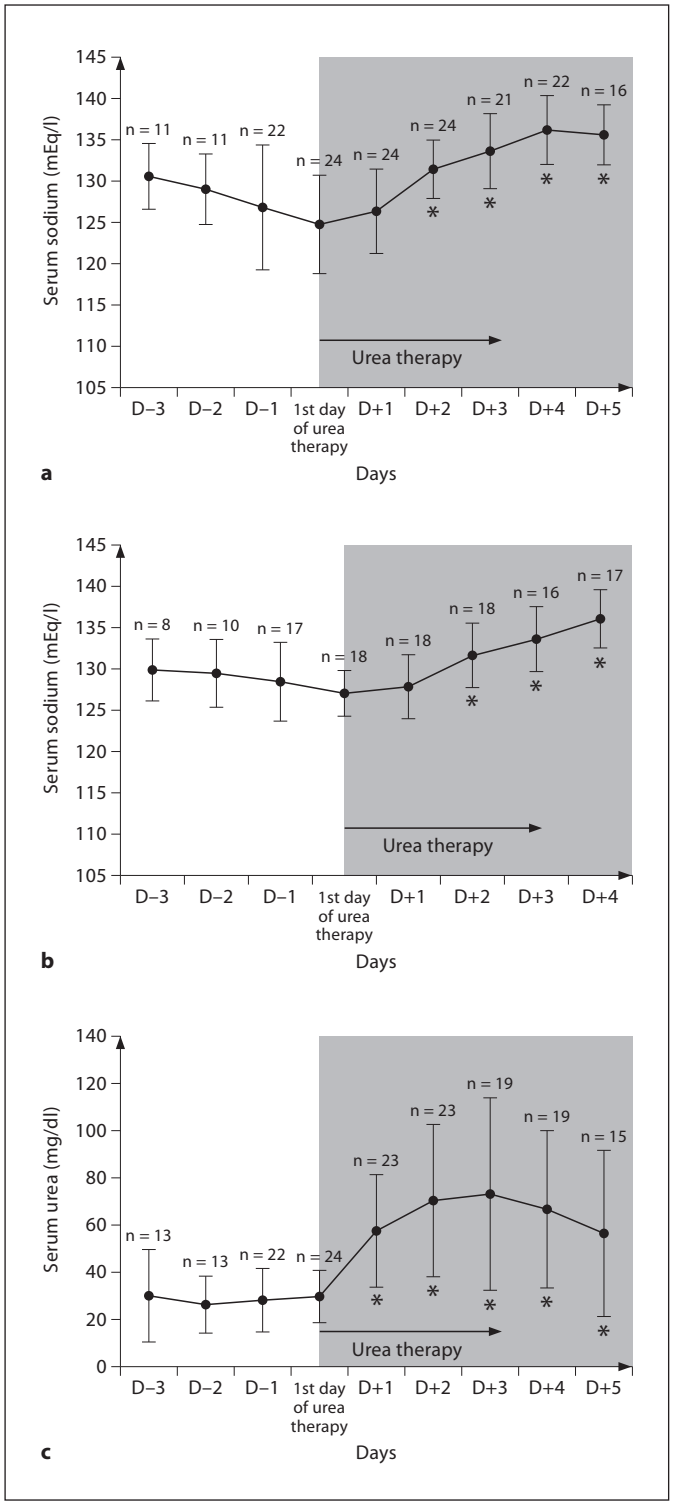

Fig. 2. a Time course of serum Na concentration during urea therapy in the 24 patients. **b** Time course of serum Na concentration during urea therapy in the 18 neurological patients. **c** Time course of serum urea concentration during urea therapy. Data are expressed as mean ± SD. * Significant increase in serum sodium treatment ($p < 0.05$). n = Number of data analyzed.

Only 2 of our patients presented Na <115 mEq/l (99.7 and 110.1 mEq/l). Contrary to the 22 other patients who developed hyponatremia during the ICU stay, these were the 2 patients admitted to our ICU for neurological symptoms related to SIADH. In these 2 patients, correction of serum Na was inferior to 10 mEq/l/24 h (6.3 ± 2.7 mEq/l/24 h).

In the 24 patients, mean serum urea concentration also increased (from 29.8 ± 11.1 mg/dl before urea prescription to 57.6 ± 24.0 mg/dl on the first day of treatment and 73.2 ± 41.0 mg/dl on the third day of treatment, both $p < 0.001$) (fig. 2c). The change in serum Na between day 0 and day 3 of treatment was positively and significantly correlated to the simultaneous change in serum urea concentration in the 24 patients ($r = 0.551$, $p < 0.01$).

Of the patients hospitalized with cerebral injury (n = 18), 8 underwent intracranial pressure monitoring but only 2 had the intracranial pressure monitor in situ at the time they received urea. The limited data did not demonstrate any effect of urea treatment on intracranial pressure.

No side effects related to urea therapy were noticed during the ICU stay. In particular, no case of osmotic demyelination syndrome (ODS) was observed.

Discussion

Our data show that urea seems to be a rapid and effective treatment for SIADH-associated hyponatremia in ICU patients. Urea administration led to a rapid and significant increase in serum Na concentration in these 24 patients, independently of the etiology of the disorder. This treatment has been known for many years to be effective as a treatment for chronic SIADH, and is commonly used for this purpose [15]. A recent study reported the beneficial role of administration of urea in SIADH in ICU patients. Indeed, only Decaux et al. [16] showed recently that urea therapy combined with isotonic saline is a useful, safe and inexpensive option to treat euvolemic hyponatremia. In this study, we confirmed the results of the study by Decaux et al. [16]. Indeed, we observed the same increase in mean serum Na concentration (7 mEq/l in 48 h) with a similar posology of urea (45 g/day). In addition, we also observed good results in patients with severe hyponatremia (Na ≤127 mEq/l), as observed by Decaux et al. [16]. These authors recalled that vaptans have not been well studied in these patients. Then, unlike the vaptans, which are very ex-

pensive, the low cost of urea therapy should encourage physicians to use it.

Urea $CO(NH_2)_2$ is a small, soluble and diffusible molecule of 60 Da, synthesized by the liver, that is the major end product of protein catabolism. This molecule is freely filtered by the glomerulus. It constitutes a large osmotic load to the kidney. In subjects consuming a typical Western diet, this molecule is the most important osmotic substance in the urine, in which it represents about 50% of the urine osmolality, whereas it represents only 2% of the plasma solutes [20, 21]. In normal conditions, urea plays an important role in the urinary concentrating process by its participation in the countercurrent exchange system, in which a renal urea recycling mechanism enables large quantities of urea to be excreted without obligating water excretion [22]. It therefore spares water and permits a high concentration of urea in the urine.

In our patients, however, the doses of urea administered were relatively large (45 g of urea represent 750 mosm, approximately doubling the daily osmotic load provided by a normal occidental diet). As recently recalled by Berl [23], the kidney's capacity to excrete solute-free water is markedly improved by an increment in solute intake. Thus, the large additional osmotic load brought by urea improved the ability of SIADH patients to correct their excess total body water. Besides, the most efficient urine concentration is known to be achieved for a ratio of urea to non-urea solutes in the range of 20–120% [21]. In our patients, the higher proportion of urea in the urine probably induced a moderate osmotic diuresis by disturbing the osmotic gradient in the medulla and thus reducing urine concentration [15]. Finally, urea administration tends to decrease Na excretion as a result of the complex interaction between urea and Na in the urinary concentrating mechanism [21]. This could lead to some Na retention [15] and thus also contribute to the correction of hyponatremia [21].

Hypoosmolar hyponatremia can cause brain swelling as water shifts from the extracellular into the intracellular fluid compartment. Depending on the severity and duration of hyponatremia, this may result in signs or symptoms of cerebral edema, including visual and focal neurologic changes, encephalopathy and seizures. Ultimately, brain herniation can occur. These patients need to be assessed quickly because those with serious neurologic signs or symptoms thought to be related to hyponatremia require urgent treatment. Urea could be an effective treatment in such patients. Regrettably, only 2 of our patients had intracranial pressure monitoring at the time of the urea therapy. Further studies, looking at the time course of intracranial pressure during correction of hyponatremia with urea treatment, are needed to confirm the real advantage of this treatment in such patients.

Besides, because of the risk of ODS in case of rapid (excessive) correction of hyponatremia, management needs to be careful in these patients. No cases of ODS were observed in our study, as in other studies with urea. Only 2 of our patients presented a hyponatremia <115 mEq/l, in which most of the ODS cases are reported. Moreover, in these 2 patients, correction of serum Na was inferior to 10 mEq/l/24 h (6.3 ± 2.7 mEq/l), avoiding brain demyelinating lesions. Furthermore, Soupart et al. [24] described that treatment of hyponatremia by urea may protect the brain against ODS in rats. The authors interpreted the resistance of uremic brain against ODS as the consequence of its ability to more quickly reestablish its intracerebral organic osmolyte contents [24].

There are several limitations of our study that should be considered when interpreting our results. First, the impact of self-correction of the hyponatremia, and the relative contributions of urea therapy, saline infusions and fluid restriction are difficult to establish due to the retrospective aspect of the study. Nevertheless, urea therapy was initiated sometime after the diagnosis of SIADH (median delay of 2 days), suggesting that fluid restriction and saline infusions alone were not able to self-correct the hyponatremia. Second, we cannot be certain that the patients we included did not have a RSWS rather than a SIADH. The existence of the RSWS is controversial as suggested recently by Brimioulle et al. [25] who demonstrated no difference in red blood cell, plasma and blood volumes between hypo- and normonatremic ICU patients. Even if the existence of this entity remains under debate due to conflicting conclusions from different studies, treatments are theoretically opposite with infusion of fluids and Na in the salt-wasting syndrome and fluid restriction for SIADH. Nevertheless, it should be recognized that the absence of correction of mean serum natremia with Na infusion is an important argument against RSWS in our patients. Clinical assessment of extracellular volume status, which is crucial to precise the etiology of hyponatremia, is difficult and limited by the retrospective design of this study. In our study, 50% of the neurological patients (9/18) had an acid uric value analyzable at the time of the diagnosis. All of them had a low serum uric acid level, but acid uric levels are thought to be low in both SIADH and RSWS [10]. Only measurement of blood volume, persistence of hypouricemia or increased fractional ex-

cretion of urate after correction of hyponatremia seem able to distinguish these two entities [10]. These data were not collected in our study, and should be collected in further prospective studies.

In conclusion, urea administration appears to be a safe and useful treatment for SIADH-associated hyponatremia in critically ill patients. The low cost of this treatment in comparison with vaptans should encourage its use. Nevertheless, a prospective study is needed to further evaluate the effects of urea therapy in the ICU and comparison of urea with vaptans in SIADH-associated hyponatremia could be performed in ICU patients to fully define the use of this 'old' medicine in today's critical care setting.

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Disclosure Statement

The authors have no conflicts of interest to disclose. The results of this paper have not been published previously except in abstract form in French [Réanimation 2011;20(suppl 1):SP246].

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