



SHORT REVIEW

Urea for management of the syndrome of inappropriate secretion of ADH: A systematic review[☆]



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Received 26 January 2014; accepted 15 April 2014

Available online 18 October 2014

KEYWORDS

Urea;
Syndrome of
inappropriate
secretion of
antidiuretic hormone;
Hyponatremia;
Systematic review

PALABRAS CLAVE

Urea;
Síndrome secreción
inadecuada hormona
antidiurética;
Hiponatremia;
Revisión sistemática

Abstract Urea has been recently proposed for the management of hyponatremia linked to the syndrome of inappropriate secretion of ADH (SIADH). The objective of the study was to review the levels of evidence for treatment of hyponatremia associated with SIADH with urea. We performed a systematic review of experimental trials and grading according to SIGN. No clinical trials were found. The 6 studies analyzed had methodological limitations and were prone to biases. In conclusion, there is no evidence to support the efficacy of urea for the treatment of hyponatremia following SIADH.

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La urea en el manejo del síndrome de secreción inadecuada de la ADH: una revisión sistemática de la literatura

Resumen Recientemente se ha propuesto el uso de la urea como tratamiento complementario en el síndrome de secreción inadecuada de la ADH (SIADH). El objetivo del estudio es realizar una revisión de los niveles de evidencia de la urea en el tratamiento de la hiponatremia asociado al SIADH. Se realizó una revisión sistemática de la evidencia a partir de estudios experimentales de acuerdo con la escala propuesta por SIGN. No se encontraron ensayos clínicos. Los 6 estudios analizados presentan carencias metodológicas importantes y están muy sujetos a sesgos. En conclusión, no existe evidencia que sustente el uso de la urea en la hiponatremia asociada al SIADH.

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[☆] Please cite this article as: de Solà-Morales O, Riera M. La urea en el manejo del síndrome de secreción inadecuada de la ADH: una revisión sistemática de la literatura. Endocrinol Nutr. 2014;61:486–492.

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Antidiuretic hormone (ADH) regulates water excretion by the kidneys through interaction with three types of receptors (V_{1a} , V_{1b} , and V_2). The so-called syndrome of inappropriate secretion of ADH (SIADH) is characterized by abnormally high ADH levels, which result in excess water reabsorption, increased sodium excretion, and hyponatremia.¹ Etiology of SIADH is variable, and its main causes include some central nervous system (CNS) disorders, tumors caused by ectopic secretion, or some drugs, but approximately one third of cases are of unknown cause (idiopathic SIADH).^{2,3} Diagnosis of SIADH is confirmed by showing high urine osmolality together with low plasma osmolality in the absence of diuretics.

Hyponatremia secondary to SIADH is a common and life-threatening complication, especially in hospitalized patients. Hyponatremia is defined as blood sodium levels less than 135 mmol/L. Levels ranging from 130 to 134 mmol/L are considered as mild hyponatremia, levels ranging from 120 to 130 mmol/L as moderate hyponatremia, and levels less than 120 mmol/L suggest severe hyponatremia. Depending on the speed with which hyponatremia occurs, it may be considered as acute (<48 h) or chronic (>48 h).⁴ Symptoms usually occur when hyponatremia is severe, and may include anorexia, vomiting and confusion, followed by seizures, coma, and death.⁵

Several treatment modalities for acute and chronic SIADH are reported in the literature. If the underlying cause of SIADH cannot be corrected, the main alternatives include water restriction or correction of hyponatremia through salt intake or drug treatment with demeclocycline, lithium, urea, phenytoin, or vaptans.⁶ Water restriction is the classical therapeutic option in SIADH management, but is associated to low compliance, and additional alternatives are therefore often required.⁷

Oral or intravenous treatment with urea has been for years a known alternative for management of SIADH-induced hyponatremia, but it is not widely used in standard clinical practice because of the scarce evidence supporting its efficacy and safety in this group of patients. The few studies reported comparing the different drug treatments and the fact that the available evidence comes from studies with small patient samples or series of cases make it difficult to take decisions on the most adequate treatment for SIADH management.

In order to assess the grade of evidence supporting use of urea to treat SIADH, and to establish whether this should be considered as a valid therapeutic alternative, a systematic search was made in the literature available, and its results were reviewed using objective assessment criteria. This report summarizes the methods used and the results achieved, as well as the conclusions drawn from the critical analysis of the studies reviewed.

Methods

A systematic search of the literature available about SIADH management with urea was conducted. For this, the PubMed, Trip Database, and Medify websites were consulted (with no time restrictions). Because of the scarcity of literature, wide description criteria were decided, and the following search criteria were established:

("Inappropriate ADH Syndrome" OR "Hyponatremia") AND "Urea/therapeutic use".

The initial criteria for including articles in the review were as follows: efficacy and/or safety studies in humans that were empirical or analytical in nature with a level of evidence ranging from 1++ to 2— according to the criterion of the Scottish Intercollegiate Guidelines Network (SIGN),⁸ i.e., meta-analyses, clinical trials, systematic reviews, and cohort or case and control studies.

In an exploratory analysis, 112 articles were located in PubMed, 26 in Trip Database, and 23 in Medify. Twenty-three studies addressed the matter at hand, but none of them included a control group, which limited compliance with inclusion criteria. In order to advance in the review, it was decided to also include all observational (prospective) studies conducted with a study protocol, including reviews of clinical histories (retrospective), in which results were given with statistical parameters, although the fact that they were non-controlled studies limited their validity.

Two independent raters performed data search and extraction from the articles and subsequently shared their results. Results of the search and level of recommendation of the evidence are provided.

Narrative reviews and case reports were excluded from the review because their level of evidence was lower than 2.

Results

Results of the systematic search

Seven studies met the inclusion criteria established. One of these⁹ met the methodological criteria for inclusion in the review, but was excluded because it included patients with hyponatremia due to different causes, of which SIADH was not the only one.

Of the six articles finally included in the review, none met the characteristics of a randomized clinical trial.^{10–15} A single article¹³ was an experimental study with an active comparator. The study compared the efficacy, tolerability, and safety of treatment with urea as compared to vaptans. The study was not designed with two parallel arms, but had a single arm with sequential treatment periods (one year on vaptan treatment followed by an 8-day washout and one year of treatment with urea). All other studies, observational in nature, had a limited validity because most of them were descriptive studies based on reviews of clinical histories with no control group, and their conclusions are therefore not free from bias.

The six studies reviewed encompassed a total of 178 patients, part of which received acute treatment with urea and other chronic treatments, but an active comparator was not used in all cases. Except for the Decaux et al. study (2010), where the clinical histories of 85 patients were reviewed, all studies were conducted on small numbers of patients (7–24).

Table 1 lists the studies reviewed and their validity (level of evidence). The level of evidence of the reviewed studies was low, mainly level 2— in the SIGN scale.

Table 1 Studies included in the critical review (SIGN).

Reference	Study design, n	Level of evidence
(1) Soupart 2012 ¹⁴	Prospective, non-randomized study with no control group n = 13 patients (12 completed the study) Treatment with vaptans (1 year), followed by urea (1 year)	2+
(2) Coussement 2012 ¹⁰	Observational, retrospective study with no control group n = 24 patients treated with urea at an intensive care unit	2–
(3) Decaux 2010 ¹¹	Observational, retrospective study with no control group in 2 patient groups: n = 50 patients with mild hyponatremia treated with urea n = 35 patients with severe hyponatremia treated with urea and isotonic saline	2–
(4) Decaux 1982 ¹²	Observational, prospective study with no control group n = 7 patients	2–
(5) Decaux 1981 ¹³	Observational, prospective study with no control group n = 7 patients	2–
(6) Perrakos 2012 ¹⁵	Prospective review of 42 patients with SIADH after subarachnoid hemorrhage administered urea	2–

Synthesis of evidence

Table 2 summarizes the main results of the reviewed studies. Their analysis shows that treatment with urea has been evaluated in both acute and chronic hyponatremia. In all studies, patients had SIADH from different causes (associated to CNS disorders or carcinoma, or idiopathic, among other causes).

The Soupart study¹³ was the only one in which an attempt was made to establish differences of efficacy between chronic treatment with urea and a comparator, in this case satavaptan (n = 10) and tolvaptan (n = 2) grouped under the generic therapeutic class of vaptans. Thirteen patients started the study on a fixed dose of vaptans. One patient withdrew from the study during the tolvaptan treatment period and was excluded from the statistical analysis. After one year of treatment with vaptans, the remaining 12 patients underwent an 8-day washout and started treatment with urea. During the washout period, patients returned to a hyponatremia level similar to that at study start. At the end of the two annual periods, patients achieved blood sodium levels of 135 mEq/L with both types of treatment.

In all studies reviewed, sodium level was restored in patients treated with urea in some hours to several days, and sodium levels were maintained within normal values over time (sodium level of approximately 135 mEq/L). However, in the Decaux study,¹² including 7 patients with chronic SIADH, a fluctuating response was seen between patients (sodium levels after one week of treatment with urea ranged from 132 to 141 mEq/L) and for a same patient over time.

In most studies, urea was administered according to standard clinical practice, with the resulting differences in dosage (15–120 g/day), administration route (oral, intravenous or through a gastric tube), treatment periods (ranging from several days and one year), and interactions with other treatments (water restriction, saline, salt supplements, and drugs for the underlying disease). A standard scheme for SIADH treatment with urea cannot be drawn from

the review of these studies, and the results achieved cannot be attributed only to urea or the sum of regimens given to each particular patient.

In this regard, authors of the 1981 Decaux study¹³ related the fluctuations in results seen in their study to the volume of water ingested by patients, which may reflect that the results achieved in the studies are not only related to the effect of urea. One study¹³ stated that treatment of the underlying condition, in this case with chemotherapy, relieved SIADH in 2 of the 4 patients with carcinoma, and treatment with urea could therefore be discontinued. All other studies included no explicit information about concomitant treatment for the underlying disease or the potential influence of other treatments on the final result.

Two patients experienced headache after administration of a dose, but the most common adverse events were hypokalemia and hypernatremia. Hypokalemia was reported in a single study, but with a frequency of 7 out of the 35 patients with severe SIADH in the 2010 Decaux study¹⁰; in this group of patients, a trend to recurrence (6 of the 35 patients) was also seen after treatment discontinuation. Hypernatremia was found in one of the 12 patients in the Soupart study and in 7 of the 50 patients with moderate SIADH in the 2010 Decaux study. Overall, authors concluded that urea was well tolerated, and no study reported serious adverse events. However, some studies provide little or no information, and when specific information is given, hypokalemia and hypernatremia are reported in up to 20% and 14% of patients respectively. In any case, the numbers of patients and the design of studies reviewed make it difficult to draw conclusions about the frequency and actual significance of such adverse events.

Discussion

Although management of hyponatremia associated to SIADH with urea has repeatedly been suggested, the evidence supporting this approach is far from convincing. Studies

Table 2 Summary of the results of studies included in the review.

Reference	Patient characteristics	Treatments and dose	Follow-up time	Baseline sodium level	Results
(1) Soupart 2012 ¹⁴	Twelve hospitalized patients with chronic SIADH of different causes (13 patients at study start; one patient discontinued vaptan treatment)	- Vaptans (satavaptan 5–50 mg/day, n = 10; tolvaptan 30–60 mg/day, n = 2) - Oral urea 15–30 g/day Water intake no higher than 1500–2000 mL/day was recommended	Chronic treatment Study duration: 2 years (1 year of treatment with vaptans followed by 1 year with urea)	Baseline level: 125 ± 3 mEq/L Level after 8-day washout: 126 ± 5 mEq/L	Sodium level after the vaptan period: 135 ± 3 mEq/L. One patient discontinued the study due to excess thirst Sodium level after the urea period: 135 ± 3 mEq/L. One patient experienced uncomplicated hyponatremia
(2) Coussement 2012 ¹⁰	24 patients in the intensive care unit with SIADH of different etiologies	ND	Acute treatment	124.8 ± 5.9 mEq/L	Blood sodium levels significantly increased from the second day of treatment (131.4 ± 3.5 mEq/L, $p < 0.001$), and normalized after 4 days of treatment (136.2 ± 4.1 mEq/L, $p < 0.001$).
(3) Decaux 2010 ¹¹	Patients at an intensive care unit with euvoletic hyponatremia: (I) 50 patients with moderate hyponatremia (II) 35 patients with severe hyponatremia	(I) Urea, oral or through gastric tube, 15–120 g/day (mean dose 46.25 g/day) (II) Urea, oral or through gastric tube (0.5–1 g/day), together with saline	Treatment: (I) Mean duration, 6 days (2–42) (II) Mean duration ND	(I) 128 ± 4 mEq/L (II) 111 ± 3 mEq/L	(I) Increase in sodium level at 2 days of treatment (135 ± 4 mEq/L, $p < 0.001$) with normal water intake (>2 L/day). Seven patients experienced hyponatremia. Six patients recurred on treatment discontinuation. (II) Increase in sodium level after one day of treatment (122 ± 4 mEq/L, $p < 0.001$). There were no cases of hyponatremia. Seven patients experienced hypokalemia

Table 2 (Continued)

Reference	Patient characteristics	Treatments and dose	Follow-up time	Baseline sodium level	Results
(4) Decaux 1982 ¹²	Seven patients with severe hyponatremia secondary to SIADH of different etiologies	Oral or intravenous urea 60–90 g/day + water restriction (500 mL) + salt supplements as needed	Acute treatment	117 ± 2 mEq/L	Sodium levels increased to 126 ± 1.4 mEq/L in 8 h ($p < 0.01$), 130 ± 1.3 mEq/L at 12 h ($p < 0.01$), and 134.5 ± 1.2 mEq/L at 24 h ($p < 0.001$) One patient reported headache after urea infusion
(5) Decaux 1981 ¹³	Seven patients with chronic SIADH of different etiologies* intolerant to water restriction (sodium level <125 mEq/L after water restriction for 5 days) *3 patients with brain disorders, 4 patients with carcinoma	Oral urea 30–60 g/day Water intake no higher than 2 L/daily was recommended	Chronic treatment (10–270 days)	115 ± 6 mEq/L	Chemotherapy relieved SIADH in 2 of the 4 patients with carcinoma, who were discontinued urea treatment. Mean sodium level was 136 ± 3.5 mEq/L after one week of treatment (132–141 mEq/L) Sodium level fluctuated over time in relation to fluid intake However, patients on long-term treatment with urea remained symptom-free during treatment One patient reported headache after a urea dose
(6) Perrakos 2012 ¹⁵	42 patients with history of subarachnoidal hemorrhage who experienced SIDH at a single center	Oral urea 15–30 mg/6–8 h dissolved into 50 mL of water (max 180 mg/day) until Na levels >135 mEq/L are achieved for >48 h	Acute treatment	139 ± 3 mEq/L	Treatment was started 7 (IQR, 5–10) days after admission, with plasma Na increases on the first day of 3 (IQR, 1–6) mEq/L and a time to Na ⁺ >130 and >135 mEq/L of one (IQR, 1–2) and 3 (IQR, 2–4) days respectively

on the subject are few and heterogeneous, and a standardized treatment regimen cannot therefore be established from the available evidence. Despite the evidence derived from non-controlled studies, the sample size and design of studies reviewed do not allow for drawing conclusions or grades or recommendation on the tolerability of urea, and researchers themselves stated in their discussions that both the evidence and experience with use are limited and should be adequately established.

The efficacy, safety, and tolerability data on urea treatment have not been evaluated in any randomized clinical study, or even in a controlled cohort study. The available evidence on the results is not only scarce, but also based on reports of treatment in actual clinical practice or on prospective studies with no control group. Thus, the level of evidence of published articles ranges from 2– to 3 according to SIGN criteria, except for a study where the level of evidence could be considered 2+.

We should therefore agree with authors when they state that the evidence gathered suggests a benefit. Variability exists however in efficacy and the time to occurrence of benefit and its duration. With regard to validity of results, it should also be noted that disparity exists in both results and the population enrolled, which makes it difficult to issue recommendations with adequate external validity.

Several sources of confounding that are not adequately reported or analyzed in the studies have been detected, including: (a) daily dose of urea, which was quite variable between patients in some studies; (b) administration time; and (c) interaction of urea with other treatments with an impact on sodium level, such as treatment of the underlying cause, water restriction, saline, or salt supplements.

In all 6 studies included in the review, use of urea was related to restoration of sodium levels. While these results provide an indication of the effectiveness of urea for SIADH management, the general design of the studies was biased, which makes it difficult to establish clear causal relationship between the tested treatment and the result achieved. Authors themselves emphasized in their conclusions that results of their studies have to be confirmed in randomized, controlled clinical trials. Although good tolerability was usually reported, the events of headache, hypokalemia, and hypernatremia occurring in some studies appear to suggest that the treatment is not free from adverse events.

Finally, we may wonder how should a nutritional supplement such as urea be incorporated, and whether it should be included or proposed in treatment guidelines. First of all, and based on the foregoing, it appears clear that there is no evidence that allows for ensuring the efficacy (effectiveness) of the treatment. A gap appears to exist in the regulations as regards use of these substances for the treatment of medical diseases. As they are not registered as drugs, they are not subject to the applicable regulations as regards manufacturing, dosage, or other aspects that would be considered relevant for managing diseases which are life-threatening or induce excess mortality.¹⁶ While present in multiple treatments, urea per se has no recognized health according to the EU regulations, and its benefits for health cannot therefore be promoted. Its use is therefore left to the discretion of the physician.

Conclusions

The critical review of the available literature on management of patients with SIADH using urea does not allow for showing the efficacy and tolerability of treatment with urea with any certainty, because it has only been assessed in non-randomized clinical studies with biased designs and using variable doses and administration intervals. There are no studies that allow for analyzing urea safety or interaction with other treatments with and without effects on sodium levels.

Based on the available evidence, use of urea for the treatment of hyponatremia associated to SIADH should not be recommended beyond the opinions of “experts”, although the level of evidence is low.

Conflicts of interest

OSM has received fees and grants from multiple pharmaceutical companies, including Otsuka Pharmaceutical, Astellas Pharma, and Sanofi-Aventis.

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