Beneficios de la urea oral en pacientes con hiponatremia e insuficiencia cardiaca

Benefits of oral urea in patients with hyponatremia and heart failure.

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ABSTRACT

Objectives: To assess the efficacy and safety of oral urea in patients with hyponatremia and heart failure (HF).
Methods and Results: This is a retrospective observational study of hospitalized and non-hospitalized patients with HF and hyponatremia (serum Na+ < 135 mEq/L) followed by the Heart Failure Unit between January 2013 and May 2018. The study evaluated sodium normalization levels (Na+ = 135 ± 3 mEq/L) after treatment with oral urea. Thirty-four patients were included in the study, and all were on standard treatment for HF. Natremia at the beginning of treatment with oral urea was 126.34 ± 5.41 mEq/L, and the mean on the day of normalization was 136.45 ± 3.22 mEq/L ($p < 0.001$). The mean time to achieve sodium normalization was 4.28 ± 2.37 days. Blood urea at the beginning of treatment with urea was 85.77 ± 50.51 mg/dl, and the mean on the day of Na+ normalization was 137.90 ± 56.66 mg/dl ($p < 0.001$). There was an increase in diuresis ($p < 0.006$) and plasma osmolarity ($p < 0.001$) as well as a slight decrease in serum potassium ($p < 0.001$). The mean dose of oral urea was 22.5 g/day. There were no important adverse effects, nor were there significant changes in creatinine levels or the estimated glomerular filtration rate by the MDRD formula.
Conclusions: When added to the standard treatment for short periods of time, treatment with oral urea is safe and effective at correcting natremia and improving diuresis in patients with hypervolemic HF with hyponatremia.

Keywords: Heart failure, hyponatremia, oral urea, diuresis, tolvaptan, natremia.

INTRODUCTION

Hyponatremia (serum sodium below 135 mEq/L) is the most frequent electrolyte alteration in patients with heart failure (HF). It is present in 13 to 15% of cases in patients with both reduced and preserved ejection fraction and in outpatients[1] and hospitalized patients[2]. This alteration is considered a marker of poor prognosis; it is associated with an increase in the number of rehospitalizations, hospital stay, and long-term morbidity and mortality, and there is a significant inverse relationship between natremia and mortality[3-5]. Patients with hyponatremia also respond poorly to treatment and require higher doses of diuretics to reach the same level of diuresis as patients with normonatremia, especially those with sodium levels below 130 mEq/L[6].

The decrease in cardiac output and arterial inflow in HF results in neurohormonal activation of the sympathetic nervous system (SNS), activation of the Renin-Angiotensin-Aldosterone system (RAAS), and greater release of antidiuretic hormone (ADH)[7,8], resulting in hyponatremia.

Many studies in the literature have analyzed the use of oral urea to treat the syndrome of inappropriate ADH secretion (SIADH). Since 2014, the European guidelines for hyponatremia recommend oral urea as second-line treatment after water restriction in this syndrome[9-11]. Because urea acts as an osmotic diuretic and one of the pathophysiological mechanisms of hyponatremia in HF is an increase in ADH activity, we propose the use of oral urea to treat hyponatremia in HF.

We systematically reviewed the literature and did not find evidence on the use of oral urea to treat hyponatremia in patients with HF. Thus, in this study, we present a review of the results we obtained in a group of patients diagnosed with HF who had hyponatremia and were treated with oral urea.

MATERIALS AND METHODS

This is a retrospective descriptive observational study

Patients included in the study had HF and hyponatremia (serum Na+ <135 mEq/L) and were treated with oral urea in hospital and outpatient settings in the University Hospital Complex of Vigo and the University Hospital Lucus Augusti of Lugo from January 2013 to May 2018.

Data were collected by reviewing the electronic medical records.

The inclusion criteria were as follows

* Patients with a diagnosis of HF and hyponatremia (serum Na+ <135 mEq/L).

The exclusion criteria were as follows:

* Blood glucose > 250 mg/dl, or 180-250 mg/dl together with serum Na+ of 133-135 mEq/L on admission;
* Euvolemic and/or hypovolemic;
* Severe renal failure (glomerular filtration <30 ml/min/m^2); and
* Severe liver disease.

The objective of the present study was to achieve normal natremia, defined as Na+ = 135 ± 3 mEq/L.

Variables

The variables included clinical and sociodemographic data of patients, diuretic treatment, other concomitant treatments at the

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beginning of treatment with oral urea, and the evolution of variables related to the effect of urea (serum sodium and potassium, diuresis, plasma glucose, plasma osmolarity, plasma urea, glomerular filtration rate, systolic and diastolic blood pressure, and heart rate).
Adverse effects, mortality at 30 and 60 days, and causes of death were assessed.

Ethical and legal aspects

The study was approved by the Ethics and Research Committee of Galicia on 2017-06-20 with **Registration Code 2017/237**. Researchers followed applicable ethical and legal standards. Written informed consent to participate was obtained from all participants included in the study. The study has been developed according to the recommendations of the STROBE guidelines for observational studies.

Statistical analysis

A descriptive analysis of the data collected was performed using SPSS 19.0 software. To analyze the evolution of the variables before and after treatment with oral urea, Student's t-test was used for normally distributed paired data, and the Wilcoxon test was used when the data did not follow a normal distribution.

RESULTS

Thirty-four patients with HF and hyponatremia were included in the study.

Adding oral urea to the standard treatment achieves the normalization objective of the study (Na+ = 135 ± 3 mEq/L) by an average of 4.28 ± 2.37 days. Adding oral urea produces slow but significant increases with respect to baseline sodium at 24 hours ($p < 0.009$), 48 hours ($p < 0.001$), and up to the day of normalization ($p < 0.001$). Sodium increases were safe with no overcorrection. In total, 85.29% of patients reached the sodium normalization objective of the study, and 67.6% reached normal serum sodium levels. Only 5 patients (14. 71%) did not reach the normalization objective of the study.

Since adding urea, there were significant and clinically relevant increases in diuresis volume compared to baseline at 24 hours (an increase of 72.62%, $p < 0.002$), at 48 hours (an increase of 95.33%, $p < 0.005$), and at normalization day (increase of 96.31%, $p < 0.006$).

Adverse effects such as syncope, abdominal distension, diarrhea, nausea, vomiting, and oliguria—which were listed in the oral urea data sheet–were not reported. There were also no cases of sodium overcorrection, defined as an increase above 10 mEq/L in a 24-hour interval or 18 mEq/L in a 48-hour interval.
Regarding mortality, we observed 4 cases (11. 43%) from the start of treatment to 30 days, and there was no increase at 60 days. The causes of death were infections (1 case) and refractory HF (3 cases).

Table 1. Shows the sociodemographic and clinical variables at the beginning of treatment with oral urea.

Variables	Urea (n = 34) (%)
Age (years), mean	79.94
Sex (F:M)	24:10
Hospitalized/Outpatient	
Hospitalized	25 (73.5%)
Outpatient	9 (26.5%)
Cardiovascular Risk Factors	
HBP	29 (85.3%)
Diabetes Mellitus	16 (47.1%)
Dyslipidemia	18 (52.9%)
Atrial Fibrillation	20 (58.8%)
PHT	20 (58.8%)
Valvulopathy	27 (79.4%)
Pacemaker	5 (14.7%)
NYHA Functional Classification	
I	0(0%)
II	11 (32.4%)
III	19 (55.9%)
IV	4(11.8%)
Glomerular Filtration Rate (GFR, MDRD)	
GFR ≥ 60 ml/min/m^2	14 (41.17%)
GFR = 30 – 60 ml/min/m^2	20 (58.82%)
GFR ≤ 30 ml/min/m^2	0 (0%)
Etiology of Heart Disease	
Ischemic	11 (32.4%)
Hypertensive	16 (47.1%)
Dilated	7 (20.6%)
Ejection Fraction	
Preserved: > 50%	19 (55.9%)
Intermediate: 40 – 50%	5 (14.7%)
Depressed: < 40%	10 (29.4%)
Loop Diuretics (Furosemide)	
Oral treatment	9 (26.5%)
Mean dose = 80 mg	
Oral treatment	25 (73.5%)
Mean dose = 60 mg	
Thiazides	
Mean dose = 20.8 mg	6 (17.6%)
Spironolactone	19 (55.9%)
ACEI/ARA II	21 (61.76%)
Beta-blockers	25 (73.5%)
Digoxin	11 (32.4%)
Ivabradine	1 (2.9%)
Inotropes	0 (0%)
Albumin (g/dl, mean, SD)	3.39 ± 0.528
Bilirubin (mg/dl, mean, SD)	1.45 ± 1
Hemoglobin (mg/dL, mean, SD)	11.53 ± 1.75
Hematocrit (%, mean, SD)	35.07 ± 5.30
BNP	3 (8.8%)
(pg/ml, mean, SD)	283.33 ± 226.63
NT-proBNP	13 (38.23%)
(pg/ml, mean, SD)	7283.69 ± 8752.30

Table 2. Summarizes the evolution of the clinical and analytical data regarding the effect of oral urea; the day on which urea was started was considered day 0.

Variables	Day 0	Day of Na^+ normalization	p-value
Glucose (mg/dl) mean (SD)	130.68 ± 52.86	120.92 ± 58.68	0.346
Urea (mg/dl), mean (SD)	85.77 ± 50.51	137.90 ± 56.66	< 0.001
Creatinine (mg/dl), mean (SD)	1.19 ± 0.642	1.11 ± 0.522	0.926
GFR (MDRD), mean (SD)	66.6 ± 32.45	64.96 ± 27.45	0.629
Sodium (mEq/L), mean (SD)	126.34 ± 5.41	136.45 ± 3.22	< 0.001
Potassium (mEq/L), mean (SD)	4.59 ± 0.759	4.16 ± 0.481	0.001
Plasma Osmolarity (mOsm/kg), mean (SD)	272.72 ± 14.33	301.42 ± 12.58	< 0.001
Diuresis (ml) Mean (SD)	1322.73 ± 617.39	2596.67 ± 1101.67	0.006
Systolic Blood Pressure (mmHg), mean (SD)	123.56 ± 21.88	120.28 ± 19.06	0.452
Diastolic Blood Pressure (mmHg), mean (SD)	71.64 ± 15.52	68.64 ± 10.18	0.974
Heart Rate (bpm), mean (SD)	78.72 ± 12.79	79.83 ± 15.03	0.542

GFR: Glomerular Filtration Rate

Figure 1. Natremia correction after adding oral urea.

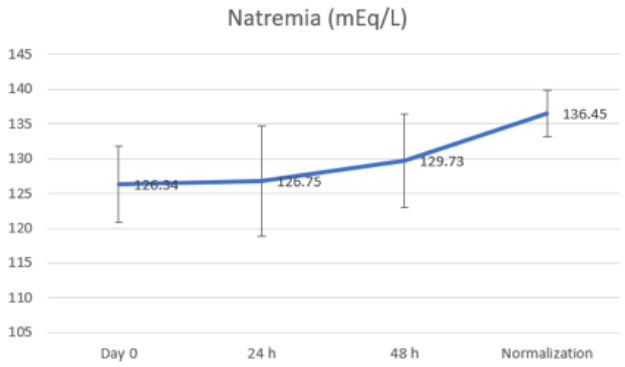

Figure 1 shows the dynamics of serum sodium concentration across time.

Figure 2. Diuresis correction after adding oral urea.

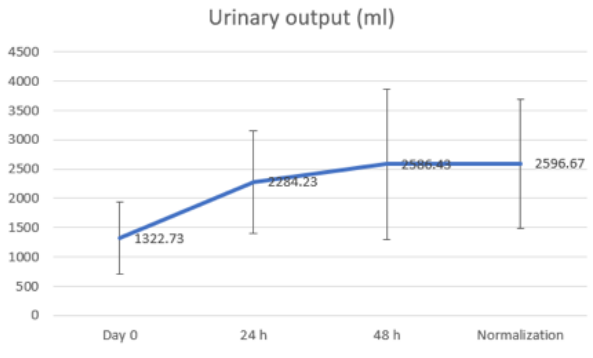

Figure 2 summarizes dynamics of diuresis volume since adding oral urea.

Table 3 shows drug safety data based on reported adverse effects.

Variables	N % (n = 34)
Adverse effects	
Asymptomatic arterial hypotension (SBP < 100 mmHg and/or DBP < 60 mmHg).	5 (14.70%)
Mild uremic encephalopathy	1 (2.9%)
Taste intolerance	1 (2.9%)

DISCUSSION

Our study sample is of real-life experience, and it is the only series in the literature on the use of urea in clinical practice to treat hyponatremia in patients with HF in hospital and outpatient settings.

Considering hyponatremia in the context of HF, we should bear in mind that its pathophysiological mechanism is not completely clear. On the one hand, the main influencing factors besides the concomitant use of diuretics are neurohormonal activation of the SNS, activation of the renin-angiotensin-aldosterone system, and inappropriate secretion of antidiuretic hormone. The SNS is activated in response to low cardiac output and decreased arterial inflow caused by HF. Low arterial inflow combined with peripheral and renal vasoconstriction results in RAAS activation. The activation of these mechanisms, together with the response to insufficient arterial inflow, produces an increase in ADH release. RAAS activation results in an increase in the secretion of angiotensin II and aldosterone. On the other hand, angiotensin II stimulates the thirst center, thereby increasing water intake and contributing to the increase of ADH release. Thus, plasma concentrations of ADH in HF remain high or, at least, inappropriately suppressed, although plasma osmolarity is decreased[7,12,13].

The therapeutic options currently available to treat hyponatremia in HF (water restriction, hypertonic saline, and tolvaptan) have limitations in their efficacy, safety, or both. Hypertonic saline can worsen water overload. On the other hand, water restriction is safe, but it presents compliance and efficacy problems[14]. Another alternative in these patients is tolvaptan, which acts as a competitive inhibitor of the vasopressin type 2 receptor. This high-cost drug increased sodium levels in patients with hyponatremia due to SIADH in the SALT and SALTWATER studies, and it was approved in Europe for this condition but not for HF-related hyponatremia[15,16]. Several studies have evaluated the effect of tolvaptan in patients with hyponatremia and HF, demonstrating its usefulness to increase sodium concentration and diuresis, decrease weight, and improve some congestive symptoms[17-21]. A meta-analysis from 2017 reached similar conclusions to these studies, but it stresses that tolvaptan does not reduce mortality or other adverse clinical events[22].

In the pathophysiology of HF-related hyponatremia, inappropriate ADH secretion plays an important role; therefore, because urea has been widely used in SIADH and recommended by the European Hyponatremia Guidelines as second-line treatment after water restriction, we propose the use of oral urea in patients with HF and hyponatremia. Urea is an osmotic, non-toxic, and low-cost diuretic. Its mechanism of action is an increase of its concentration in the renal medulla, which results in greater passive water reabsorption in the descending limb of the loop of Henle and consequently an increase in sodium concentration in the ascending limb, which is selectively permeable to sodium chloride. This higher sodium concentration in the ascending limb of the loop of Henle produces better sodium passive diffusion to the renal interstitium, decreasing its loss in urine. Further, because urea is an osmotic diuretic, it increases osmolar clearance in the urine, which increases water excretion due to solvent drag[10].

The main limitation for the use of oral urea has been the bad taste of the preparations. This has since improved due to the marketing of new galenical forms with fruit flavors in sachets of 21 grams containing 15 g of urea.

According to our results, oral urea was effective in normalizing serum sodium levels. Treatment began with doses of 15 g/24 h and sometimes required gradually increasing doses to achieve normal serum sodium concentration. The daily dose of urea used in our study was 22.5 ± 7.61 g (between 15 and 30 g of urea per day). The time to sodium normalization was an average of 4 days, which is similar to published studies of patients treated with tolvaptan[19,20,23,24].

We observed that the increase in sodium concentration with oral urea in our patients was generally slower than that documented in a series regarding treatment for SIADH[25-27]. This is probably because the pathophysiology of hyponatremia in HF is caused by several mechanisms and not only by excessive secretion of ADH, which would also explain the absence of cases of overcorrection in our study.

Treatment with oral urea also improved plasma osmolarity, serum potassium, and diuresis. The rise in plasma osmolarity is due to the increase in plasma sodium and urea concentrations. The decrease in potassium concentration was not clinically relevant and was due to the use of loop diuretics. The increase in diuresis, which almost doubled, is explained by the osmotic diuretic effect of urea combined with the use of loop diuretics.

Regarding the safety of oral urea, it was generally well tolerated and exhibited minimal side effects. Our patients had an average expected elevation of serum urea of 37.8% without deteriorating renal function when considering creatinine levels and the estimated glomerular filtration rate calculated by the MDRD formula. Similar safety results have been reported in other studies in which urea was used to treat SIADH[25-28].

Only one important adverse effect of mild uremic encephalopathy was documented in an individual with a low glomerular filtration rate and prior episodes of high blood urea levels (> 150 mg/dl). This event resolved within 48 hours after stopping the drug; another patient abandoned treatment due to the bad taste of the urea preparation.

Although there were no significant changes in mean heart rate and systolic and diastolic blood pressure with the addition of oral urea, there were 5 cases (14.70%) of arterial hypotension defined as systolic blood pressure <100 mm Hg and/or diastolic blood pressure <60 mm Hg at some point during treatment. The episodes of hypotension were clinically asymptomatic and did not require stopping the drug. The cause of arterial hypotension is attributed to the increase in urea-mediated diuresis together with the high doses of diuretics used.

In our study, we observed a mortality rate of 11.43% at 30 days after treatment initiation, and it did not change at 60 days. The

results reported in other series of patients with HF and hyponatremia[29,30] and in a recent study with tolvaptan[19] were similar and even exhibited higher mortality rates than our study.
The limitations of our study include the absence of a control group and small sample size. Randomized controlled studies are necessary to confirm the benefit of oral urea in patients with HF and hyponatremia.

CONCLUSION

Oral urea added to the standard treatment for short periods of time is safe and effective to correct natremia and improve diuresis in patients with hypervolemic HF with hyponatremia.

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CONFLICT OF INTEREST

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SOURCE OF FUNDING

None to declare.

ETHICAL ASPECTS

The study was approved by the Ethics and Research Committee of Galicia on 2017-06-20 with Registration Code 2017/237.
Researchers followed applicable ethical and legal standards.
Written informed consent to participate was obtained from all participants included in the study. The study has been developed according to the recommendations of the STROBE guidelines for observational studies.

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