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Urea for Chronic Hyponatremia

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Abstract
Background: Hyponatremia is the most common electrolyte disorder encountered clinically. While acute and/or severe hyponatremia is commonly associated with significant symptoms, milder and more chronic forms of hyponatremia remain clinically inconspicuous. Recent evidence suggests that even milder forms of hyponatremia are associated with increased morbidity and mortality. Despite this, currently available treatments for chronic hyponatremia lack data on efficacy and/or have important limitations related to patient nonadherence, adverse side effects, and/or significant costs. Consequently, there is a clear need for investigation of alternative treatments for this common condition. ***Summary:*** Small case series conducted in Europe since the early 1980s suggest that urea, an oral osmotic diuretic that increases urinary water excretion, is safe and effective for the treatment of chronic hyponatremia. In 2016, a novel formulation of urea became available in the United States. Our group recently reported the first and only study describing the efficacy and safety of this American formulation of oral urea among hospitalized patients with hyponatremia. ***Key Messages:*** Oral urea appears to be an effective, safe, and well-tolerated therapeutic strategy in the management of chronic hyponatremia.

Introduction

Hyponatremia, defined as a plasma sodium (PNa) concentration <135 mmol/L, is the most common electrolyte disorder encountered clinically. Hyponatremia is categorized as mild (i.e., PNa 130–134 mmol/L), moderate (i.e., PNa 120–129 mmol/L), or severe (i.e., PNa <120 mmol/L) and as acute (i.e., duration <48 h), or chronic (i.e., duration ≥48 h). The small proportion of patients with this disorder who present with severe and/or acute hyponatremia frequently have overt neurological symptoms and require hospitalization and urgent treatment. Much more commonly, patients with this condition have chronic nonsevere hyponatremia that typically does not require hospitalization or urgent therapy. While such patients are seemingly asymptomatic, a growing body of evidence demonstrates that even mild chronic hyponatremia is associated with subtle neurocognitive deficits, gait and postural disturbances, development of osteoporosis, heightened risk for falls and fractures, and increased mortality [1]. As a result, there has been substantial interest in identifying treatments that can be used for the long-term management of patients with chronic hyponatremia that are safe, well-tolerated, and that mitigate the morbidity and mortality associated with this condition.

The most common etiology of chronic hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and interventions currently used to treat this condition are based on our understanding of its

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pathophysiology. However, some of these treatments, including loop diuretics, oral sodium chloride tablets, and fluid restriction (FR), lack evidence of efficacy from clinical trials, and in the case of FR, pose significant challenges to long-term patient compliance. Other therapies such as vasopressin antagonists (i.e., vaptans) have been shown to improve PNa in clinical trials [2], yet their widespread use is limited by the notable risk for serious side effects, including liver injury, risk of overly rapid correction of PNa, as well as very high costs. Consequently, at present, there are no treatment interventions available that have been shown in clinical trials to be efficacious, safe, easy for patients to adhere to, and affordable for long-term use.

Small case series conducted in Europe [3–7] have investigated the efficacy of increasing urinary solute excretion through the administration of oral urea and found this agent to be safe and effective for the treatment of hyponatremia. Moreover, oral urea has not been available for clinical use in the United States until recently when Ure-Na™, a novel commercial formulation was introduced. An intravenous urea formulation (Ureaphil) was available in the early 1960s for the treatment of elevated intracranial and intraocular pressure (given the osmotic properties of urea), but its use faded with the introduction of mannitol. Ureaphil was eventually discontinued in 2006. This review describes the pharmacology of urea, the evidence for its efficacy in hyponatremia, its adverse events, indications, contraindications, and practical recommendations for use in the management of chronic SIADH.

Pharmacology of Oral Urea

Pharmacokinetics

Over 90% of oral urea is absorbed in the upper gastrointestinal tract with <4% reaching the colon where it is metabolized into ammonium by bacterial ureases. Urea distributes in total body water. In general, urea behaves as an ineffective osmole as it crosses cell membranes rapidly penetrating muscle tissue and reaching steady-state concentrations within 1 h. However, urea's permeability across the blood brain barrier is much less and can take up to 10 h to penetrate brain tissue therefore urea here is considered a partially effective osmole [8]. The latter explains why urea was used as an osmotic agent for elevated intracranial pressure and intraocular pressure in the past. The half-life of oral urea is approximately 2 h. A dose of oral urea is excreted in the urine within 12 h [9].

Renal Handling of Urea

Urea is freely filtered by the glomerulus. Fifty percent of filtered urea is passively reabsorbed in the proximal tubule. Urea is stored in the medulla where it makes up to 50% of solutes in the inner medulla. Some urea is secreted into the thin limbs of the loop of Henle (i.e., urea recycling) so the amount of urea at the beginning of the thick ascending limb reaches 110% of the filtered urea. Urea transporter UT-A2 has been identified as the urea transporter in the thin descending limb. The renal tubule is relatively impermeable to urea from the thick ascending limb of the loop of Henle to the outer medullary collecting duct (OMCD). Nevertheless, only about 50% of filtered urea remains in the lumen at the end of the OMCD. In the presence of vasopressin, about 20% of filtered urea is absorbed through UT-A1 urea transporters in the apical membrane the inner medullary collecting duct cells. Urea then exits these cells via UT-A3 urea transporters in the basolateral membrane. The net result is that only 30% of filtered urea is excreted in the urine (Fig. 1).

Mechanism of Action of Urea in Hyponatremia

Urea, with a molar mass of 60 g/mol, works as an effective osmole (i.e., osmotic diuretic) in nephron segments with high water permeability and low urea permeability, namely, the connecting tubule, cortical collecting duct, and OMCD. The effects of urea on free water excretion can be better explained by the dependence of free water excretion on solute excretion [10] (Table 1). Furthermore, the pathophysiology of hyponatremia in SIADH not only involves dilution from water accumulation but also a component of sodium loss [11]. Urea in SIADH has been shown to decrease natriuresis and creates a state of positive sodium balance which also contributes to the improvement of PNa [12].

Efficacy of Urea in Hyponatremia

Preliminary evidence of the efficacy of oral urea derives from small case series reported in Europe since the early 1980s (Table 2). Decaux and Genette [5] studied 7 patients with chronic hyponatremia and found that treatment with urea over a period of up to 9 months resulted in an increase in mean PNa from 116 to 136 mmol/L and was not associated with any major side effects. Another study by Decaux et al. [4] of 50 patients with mild to moderate hyponatremia (PNa 120–134 mmol/L) found that 2 days of treatment with urea increased PNa by 7 ± 4

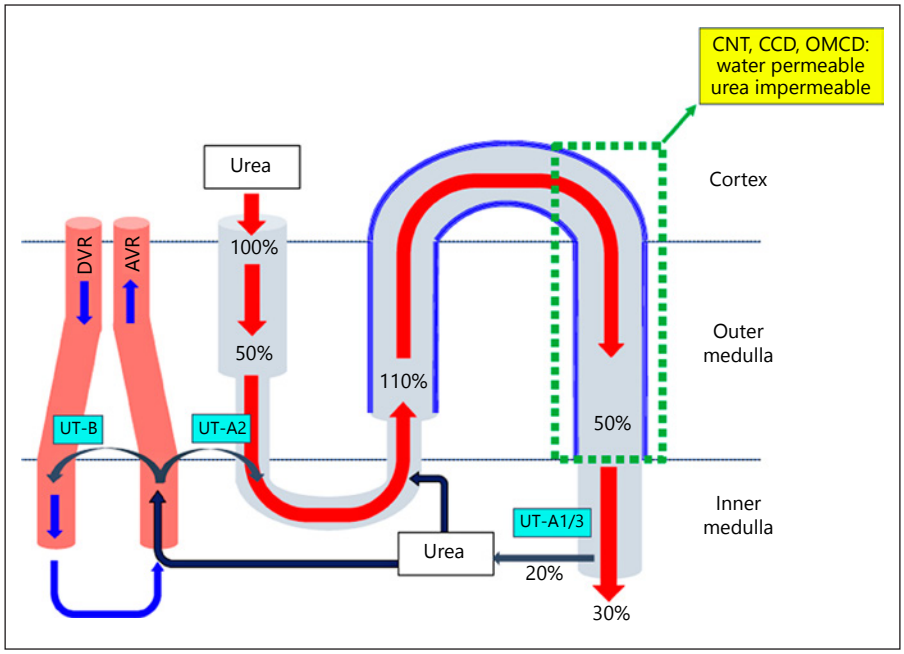

Fig. 1. Renal handling of urea. Urea is freely filtered by the glomerulus. About half of filtered urea is reabsorbed in the proximal tubule. Urea is secreted into the lumen of the thin limbs (urea recycling) increasing urea concentration at the beginning of the thick ascending limb. From there on, urea permeability is reduced until reaching the CCD but greatly increases in the presence of vasopressin in the inner medullary collecting duct. Green dotted area represents the nephron segments with high water permeability and low urea permeability where urea exerts its osmotic effects. DVR, descending vasa recta; AVR, ascending vasa recta; UT-B, urea transporter UT-B; UT-A2, urea transporter UT-A2; UT-A1/A3, urea transporters UT-A1 and UT-A3; CNT, connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct.

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Table 1. Water balance under different settings

Setting	Solute intake, mOsm/day	Water intake, L/day	Urine osmolarity, mOsm/L	Urine volume, L/day	Water balance, L/day
Normal	700	2	= 700/2 = 350	2	0
SIADH	700	2	500	= 700/500 = 1.4	+0.6
SIADH + NaCl 6 g/day	= 700+205 = 905	2	500	= 905/500 = 1.8	+0.2
SIADH + Urea 30 g/day	= 700+500 = 1,200	2	500	= 1,200/500 = 2.4	–0.4

(1) If a normal person, on solute and water balance, has a daily intake of 700 mOsm of solute and 2 L of water, then the UOsm will be a reflection of the kidneys' ability to excrete solute and water to maintain homeostasis. UOsm is the ratio between the daily mass of solutes in the urine (#Osm) and the daily urine volume (V), therefore UOsm = #Osm/V or 700/2 = 350 mOsm/L. Alternatively, V = #Osm/UOsm or 700/350 = 2 L. If the patient ingests 2 L of water daily (assuming no insensible losses) then the net daily water balance is 2–2 = 0; (2) patients with the SIADH have a "fixed" UOsm. In the example on the table, we have a patient with fixed UOsm of 500 mOsm/L with identical solute and water intake as in (1), then V = #Osm/UOsm or 700/500 = 1.4 L. The net daily water balance is 2–1.4 = +0.6 L and hyponatremia occurs; (3) If the same patient with SIADH with same "fixed" UOsm of 500 mOsm/L and same daily solute and water intake is treated with NaCl tablets 6 g/day (205 mOsm/day) then V = (700 + 205)/500 = 1.8 L. The net daily water balance is 2–1.8 = +0.2 L. (4) Finally, if the patient in (3) is treated instead with urea 30 g/day (500 mOsm/day) then V = (700 + 500)/500 = 2.4 L. The net daily water balance is 2–2.4 = –0.4 L and hyponatremia improves.

UOsm, urine osmolality; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 2. Efficacy of urea in SIADH

Study	Design	Control group	Sample size	Setting	Baseline PNa, mEq/L	PNa outcomes, mEq/L	Duration, days
Decaux and Genette [5], 1981	Observational prospective	No	7	Outpatient	115±6	136±3.5	270
Decaux et al. [4], 2010	Observational retrospective	No	(I) 50 (II) 35	ICU	(I) 128±4 (II) 111±3	(I) 135±4 (II) 122±4	(I) 2 (II) 1
Coussement et al. [3], 2012	Observational retrospective	No	24	ICU	124.8±5.9	131.4±3.5	2
Pierrakos et al. [6], 2012	Observational prospective	No	42	ICU	127±2	Change at 24 h = +3 (IQR 1–6)	5
Soupart et al. [7], 2012	Quasiexperimental	Yes	13	Outpatient	126±5	135±3	365
Rondon-Berrios et al. [13], 2018	Observational retrospective	Yes	58	Inpatient	124 (IQR 122–126)	131 (IQR 127–134)	4.5 (IQR 3–8)
Lockett et al. [14], 2019	Observational retrospective	Yes	69	Inpatient	127 (IQR 122–128)	>130 at 72 h in 64.1%	5
Nervo et al. [15], 2019	Observational retrospective	No	36	Outpatient	123±4	>135 at 60 days in 91.7%	60

PNa, plasma sodium concentration; ICU, intensive care unit; IQR, interquartile range; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

mmol/L. Collectively, these and other small studies demonstrated that urea increases PNa. However, these studies were retrospective, lacked a control group, included small numbers of patients, used a formulation of urea that is not available in the United States, and did not examine whether the effect of urea on raising PNa translates into a reduction in morbidity and/or mortality.

In 2016, Ure-Na™, a novel formulation of oral urea became available in the United States. The US Food and Drug Administration considers urea as a medical food, and therefore, does not require a medical prescription for its use. The University of Pittsburgh Medical Center incorporated Ure-Na™ into their inpatient formulary in July 2016. Our group recently published the first and only study on the efficacy of this agent for the treatment of hyponatremia in the United States [13]. We identified patients hospitalized at University of Pittsburgh Medical Center with PNa <135 mmol/L who received urea, including a subgroup with SIADH who received urea as the sole drug therapy for hyponatremia ("urea-only"). We compared change in PNa in these "urea only" patients to a matched group of patients treated for SIADH but who did not receive urea. Overall, 58 patients received urea (7.5–90 g/day) over a median of 4.5 days and demonstrated an increase in PNa from 124 to 131 mmol/L ($p < 0.001$). Among 12 "urea-only" treated patients, PNa increased from 125 to 131 mmol/L ($p = 0.001$) with a greater proportion of these patients achieving normal PNa (33 vs. 8%, $p = 0.08$). While our study was retrospective and limited to hospitalized patients, the findings support the potential efficacy of this agent. Two recent studies have also confirmed the efficacy of urea [14, 15] one of them exclusively performed in cancer patients [15].

Comparative Studies

There is a single study reported in the literature comparing urea to other therapies for hyponatremia. Soupart et al. [7] studied the efficacy, safety, and tolerability of urea compared to vasopressin antagonists in 13 patients with chronic SIADH. Patients were treated with vaptans (satavaptan and tolvaptan) for 1 year. PNa increased from 125 ± 3 to 135 ± 3 mEq/L by the end of the year. Vaptans were then discontinued, and patients were allowed to become hyponatremic again. After an 8-day washout period, oral urea was introduced and maintained for 1 year.

PNa normalized in all patients (mean PNa 135 ± 2 mEq/L). The patients tolerated urea well with no significant side effects.

Adverse Events Associated with Urea

Decaux's group that has the most experience with the use of oral urea report rates of distaste of up to 15%, but this does not affect long-term compliance with urea [16]. In a most recent study performed in cancer patients, who notably have a high prevalence of dysgeusia, only 5 patients out of 36 (14%) discontinued urea due to distaste [15]. Another recent study from Australia observed that out of 69 patients, almost 23% experienced side effects, mainly distaste, and none of them were severe. However, the distaste described in these studies occurred with a different formulation of urea [14]. Distaste is much improved with the sweet citrus flavor of the American formulation of urea. In our study, only 1 patient (1.7%) discontinued urea due to distaste, and no side effects were observed [13]. Other reported side effects associated with the use of urea include nausea, vomiting, diarrhea, and headaches [9].

Overly rapid correction of PNa with the use of urea has been reported in 2 studies. Decaux and Andres [4] describe a PNa correction >12 mEq/L in 12 out of 35 (34.2%) patients with hyponatremia from SIADH treated with urea. However, it is difficult to establish causality as 10 out those 12 patients received thiazide diuretics and volume expansion with intravenous fluids. Pierrakos et al. [6] described overly rapid correction of hyponatremia in 4 out of 42 (9.5%) patients treated with urea. In our study, no patients experienced overly rapid correction of PNa [13]. Nevertheless, even when urea is associated with some small risk of overly rapid correction of hyponatremia, there have been no reports of osmotic demyelination syndrome (ODS). Moreover, animal data suggest that urea maybe protective against ODS. Soupart et al. [17] studied rats that were induced severe azotemia, mild azotemia, or no azotemia and then underwent overly rapid correction of hyponatremia. Rats with severe azotemia had a significantly better survival and developed lesser degrees of demyelination upon brain analysis. Gankam Kengne et al. [18] studied hyponatremic rats whose PNa was overcorrected using urea, lixivaptan, or hypertonic saline. All animals developed a similar degree of PNa correction. Survival in the animals that received urea was significantly better than in the other 2 groups. Fewer animals that received urea developed ODS, and the few that did, had less pronounced neurologic manifestations compared to animals who received lixivaptan or hypertonic saline. These findings perhaps explain why the incidence of ODS in hemodialysis patients remains relatively low [19, 20]. The mechanism by which urea protects ODS is unclear. It was initially thought that urea allows for the rapid reaccumulation of osmolytes during rapid correction of hyponatremia [21]. However, a subsequent study did not confirm these findings [22].

Indications and Contraindications

Urea's main indication is the treatment of hyponatremia due to SIADH. Urea may also be used in the hyponatremia of heart failure [23, 24]. There have also been reports of the successful use of urea in the hyponatremia of cirrhosis [25, 26]. In the latter scenario, there is a theoretical risk of hepatic encephalopathy as unabsorbed urea is metabolized into ammonium in the colon [27]. Urea has also been used to treat the nephrogenic syndrome of antidiuresis, an activating mutation of the vasopressin 2 receptor where vaptans are not effective [28].

Dosing

Oral urea is administered at a dose of 0.25–0.5 g/kg/day with usual doses of 15, 30, and 60 g/day. In general, the higher the urine osmolality (a surrogate for negative electrolyte free-water clearance), the higher the urea dose needed to correct hyponatremia. Lockett et al. [14] observed in a recent study that no patients who were given a urea dose <30 g/day normalized their PNa by 72 h.

Therapeutic Approach to SIADH with Urea

The traditional first-line therapy for SIADH is FR. However, as many as 60–70% of patients with SIADH will not respond to FR alone [29]. Predictors of nonresponsiveness to FR in SIADH include a urine-to-plasma electrolyte ratio ([Urine Na + Urine K]/PNa) >1 or a urine osmolality >400–500 mOsm/kg [29–31]. Patients who are unlikely to respond to FR alone can be treated with oral urea in association with modest FR (i.e., 1–1.5 L/day). We recommend an approach that considers the likelihood of FR responsiveness based on the above parameters (Fig. 2).

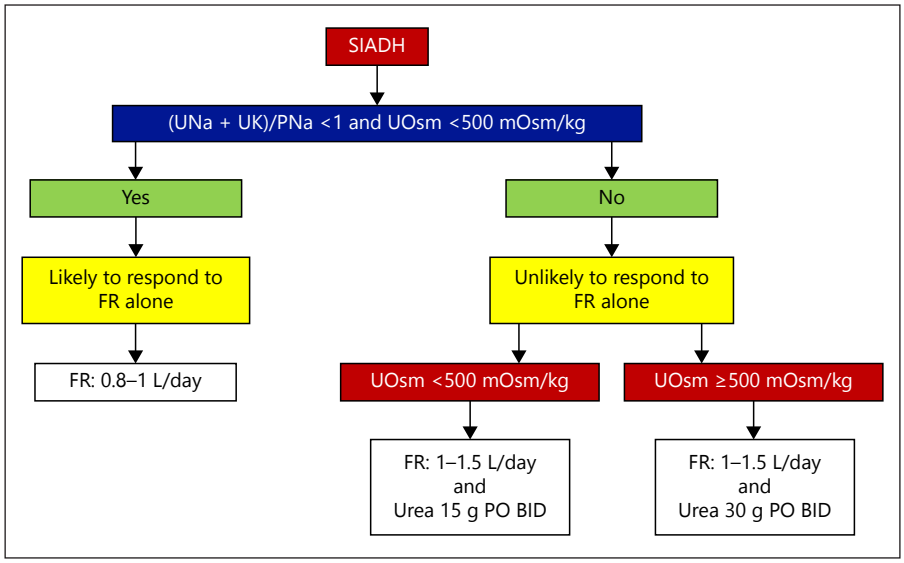

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Fig. 2. Management of chronic hyponatremia due to SIADH with urea. SIADH, syndrome of inappropriate antidiuretic hormone secretion; UNa, urine sodium; UK, urine potassium; PNa, plasma sodium; UOsm, urine osmolality; FR, fluid restriction.

Conclusions

Current therapies for chronic nonsevere hyponatremia have important limitations that preclude their widespread use. Our group and others have shown that urea appears to be an effective, safe, and well-tolerated in raising PNa. Future research is still needed to investigate the efficacy of urea for the prevention of morbidity and mortality associated to chronic nonsevere hyponatremia.

Disclosure Statement

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