

Urea for the Treatment of Hyponatremia: An Old Treatment Offers Fresh Hope

By Edgar V. Lerma and Helbert Rondon-Berrios

The conventional first-line therapy for any patient presenting with hypotonic hyponatremia due to SIAD (syndrome of inappropriate antidiuresis) is that of fluid restriction. However, we recognize that fluid restriction alone does not always work. The Expert Panel Recommendations on Diagnosis, Evaluation, and Treatment of Hyponatremia, published in 2013, identified certain criteria that are predictive of which patients are less likely to respond to fluid restriction alone (1). These include a urine-to-plasma electrolyte ratio ($[\text{urine Na} + \text{urine K}]/\text{plasma sodium [PNa]} > 1$ or a high urine osmolality ($>500 \text{ mOsm/kg H}_2\text{O}$).

It has been suggested that those patients who are unlikely to respond to fluid restriction alone may be effectively treated with oral urea in combination with fluid restriction (2).

Historically, urea was first used as a diuretic in 1892 (3). Three decades later, Crawford et al. (4) reported on its use in advanced heart failure. With the recognition of its beneficial effects on brain swelling and water excretion, in 1982, Decaux et al. (5) published their paper, which highlighted the “use of urea for the treatment of symptomatic hyponatremia in SIAD.”

For many decades, oral urea has been used for the treatment of SIAD. In fact, in 2014, the European Hyponatraemia Guideline Development Group published the

clinical practice guideline on diagnosis and treatment of hyponatraemia, which stated that “In moderate or profound hyponatraemia, we suggest the following can be considered equal second line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D)” (6).

Urea became commercially available in the United States in 2016. Unlike prescription drugs, it is regulated differently, as it does not require a prescription, and it is recommended to be used under the care of a healthcare provider. Current available formulations in the United States include ure-Na (<https://www.ure-na.com/>) and UreaAide (https://www.kidneyaide.com/about-ureaaide.html#).

In 2018, a retrospective study was published, involving an inpatient population of 58 patients, whereby it compared the change in PNa between a subgroup of patients who included those with SIAD receiving urea as the “only” medication for hyponatremia, and a matched group of patients being treated for SIAD who did not receive urea (7). In the 12 patients who received “urea only,” PNa increased from 125 to 131 ($p < 0.001$) with 33% achieving normal PNa (vs. 8%, $p = 0.08$). The study concluded that this formulation of oral urea appears to be safe and efficacious in the treatment of hyponatremia.

Other studies showed the efficacy of urea in the treatment of hyponatremia in the intensive care unit (ICU) setting (8), as well as in cancer-induced SIAD (9).

Another notable study showed that the efficacy of urea was similar to that of vasopressin antagonists for treatment of chronic SIAD, whereas tolerability was good for both agents (10).

Common side effects observed with urea include distaste, nausea, vomiting, diarrhea, and headaches (3, 9, 11). There is always a concern with rapid correction of PNa with any therapy used in hyponatremia, including fluid restriction. Two studies describe overly rapid correction associated with urea (8, 13); however, no cases of osmotic demyelination syndrome (ODS) have been reported, and there is experimental data suggesting that urea may be protective in ODS (12, 14). The main indication for urea is SIAD, and there is very limited data on its use in patients with hyponatremia associated with heart failure and cirrhosis.

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With the consideration of all of the limitations of current studies on urea for treatment of chronic hyponatremia due to SIAD, are randomized controlled trials on the horizon?

Well, in fact, a pilot study (NCT04588207) at the University of Pittsburgh, led by Dr. Rondon-Berrios, is currently in the works (15). The study plans to recruit 30 ambulatory patients with chronic non-severe hyponatremia and randomize them to oral urea or no-drug treatment for a period of 42 days. Following a 10-day washout period, participants initially randomized to no-drug therapy will receive urea, and those initially treated with urea will receive no-drug therapy for another 42 days. In addition to measuring serum sodium at baseline and after urea therapy, participants will undergo neurocognitive and posture-stability measurements. This pilot study will inform the design of a large clinical trial that will assess the efficacy of urea for the prevention of serious clinical outcomes of chronic non-severe hyponatremia. ■

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Light and Shadow in Oral Tolvaptan Treatment

By Yong Chul Kim and Hajeong Lee

Tolvaptan, an oral selective vasopressin V2 receptor antagonist, was approved by the US Food and Drug Administration (FDA) for the treatment of clinically significant hypervolemic or euvoletic hyponatremia and rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). It antagonizes the effect of an arginine vasopressin (antidiuretic hormone), which has a key role in water and circulatory homeostasis in the collecting duct of the kidney. Tolvaptan leads to an increase in urine water excretion (aquaresis) that results in enhanced free-water clearance in states of relative vasopressin excess, increasing serum sodium concentrations. Additionally, tolvaptan induces a reduction in cyclic adenosine monophosphate (cAMP), a key second messenger in the pathogenesis of ADPKD, resulting in decreased kidney cyst proliferation and fluid secretion, diminishing ADPKD cyst growth.

Two randomized, double-blind, placebo-controlled trials (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT]-1, SALT-2) demonstrated both short-term and long-term efficacy of tolvaptan in patients with hyponatremia from various causes, such as syndrome of inappropriate antidiuretic (SIAD) hormone and heart failure (1, 2). In view of ADPKD, tolvaptan slowed kidney cyst growth and functional decline with reduced frequencies of ADPKD-related complications at both early and later stages of chronic kidney disease (CKD) in two large trials: Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO 3:4) (3) and Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trials (4, 5).

Although the treatment of hyponatremia and ADPKD with tolvaptan is an important advance, there are several drawbacks. First, common adverse effects of tolvaptan should be considered, which include thirst, urination frequency, fatigue, polydipsia, and polyuria. All of these are the main causes of discontinuation during the treatment of ADPKD. Second, patients taking tolvaptan should monitor their liver function regularly due to possible drug-induced hepatotoxicity. Third, one should remain vigilant for osmotic demyelination syndrome, a rare but devastating complication arising from an overly rapid hyponatremia correction, especially if tolvaptan is used with diuretics or hypertonic

saline solution concomitantly (6). Frequent monitoring of serum electrolyte and volume status is warranted, and physicians should consider using low doses at initiation because of the potential for overcorrection (7). Forth, tolvaptan is an expensive medication, and there is a huge difference in insurance coverage by the health-care system among countries that approved tolvaptan. Currently, there are only a few studies looking at the cost-effectiveness of the treatment of ADPKD or SIAD with tolvaptan (8, 9). Last, although there is a recommendation for the timing of the initiation of tolvaptan in patients with ADPKD, it is unclear when to stop the medication. For example, do patients have to take it until dialysis? Do they quit around CKD stage 4?

Although these advances are certainly exciting and pave the way for continued investment of novel therapeutics in these areas, there are several concerns and questions about using tolvaptan in patients having either hyponatremia or ADPKD (10–12). Both require patient engagement to describe the risks and benefits before prescribing. The development of antagonists to vasopressin has ushered in a new era in clinical trials for hyponatremia and ADPKD and will hopefully only be the start of ushering in new therapies (13). ■

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