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Urea in the Treatment of Hyponatremia

HELBERT RONDON-BERRIOS, MD, FACP, FASN

Assistant Professor, Renal-Electrolyte Division

Department of Medicine

University of Pittsburgh School of Medicine

Introduction

Hyponatremia, defined as a plasma sodium (PNa) concentration less than 135 mEq/L, is the most common electrolyte disorder. Hyponatremia is associated with an increased risk of mortality in hospitalized patients.¹ It has also recently been recognized that milder, and apparently asymptomatic, forms of hyponatremia are not only associated with increased mortality, but also with an increased risk of neurocognitive deficits, gait disturbances, falls, bone fractures, and osteoporosis.² Hyponatremia also is associated with significant costs to our health care system.³

Many therapeutic interventions used in hyponatremia are supported by our knowledge of pathophysiology but are not backed by clinical trial evidence and have inconsistent efficacy, slow onset of action, and/or poor adherence.² The discovery of vasopressin receptor antagonists (VRAs) seemed to address these problems at first by providing a new drug class targeting the common denominator in most types of hyponatremias: vasopressin.⁴ Despite their demonstrated efficacy in clinical trials, the indications for VRAs in hyponatremia remain unclear.⁵ Moreover, their use has been limited by their high cost without an added mortality and/or morbidity benefit.⁶ Safety concerns have also arisen. Use of high-dose VRAs, which are not commonly used in hyponatremia, have been associated with liver injury, and now the U.S. Food and Drug Administration (FDA) warns against their use in liver disease.⁷ Also, data obtained from meta-analysis^{8,9} and case reports¹⁰ suggests that use of VRAs is associated with rapid correction of hyponatremia, and in rare cases this can result in osmotic demyelination syndrome.¹¹ Therefore, it is important to explore alternative therapies that deal with hyponatremia in a safe and cost-effective manner.

Urea has been successfully used in Europe (particularly in Belgium) for the treatment of hyponatremia since the early 1980s,¹² but it has not been available in the United States until recently, when Ure-Na™, the first commercial formulation of oral urea, was launched. Ure-Na™ comes in a sachet powder, which is mixed with water or juice. The FDA considers urea to be a medical food (GRAS category: Generally Recognized As Safe)¹³ and therefore does not require a medical prescription. This review will focus on the use of urea as a cost-effective and safe therapy for hyponatremia.

Case Presentation

A 55-year-old woman with a history of HER-2 positive breast cancer who underwent right mastectomy and radiation therapy four years prior was admitted to the hospital with a five-day history of severe back pain and nausea. Review of her systems was positive for involuntary 7 kg weight loss and persistent dry cough for the last three months. Her vital signs showed a blood pressure of 140/80 mmHg and a heart rate of 98 bpm. Her weight was 51 kg. Neck examination showed no lymphadenopathy and a normal jugular venous pressure. Lungs were clear to auscultation bilaterally. Precordial exam demonstrated a regular rhythm with normal S1 and S2, without murmurs or rubs. Abdomen was soft and non-tender. No hepatosplenomegaly was detected. No peripheral edema was present. Back examination revealed tenderness to palpation over L3 and L4 vertebral bodies. A neurological exam showed an alert and oriented woman with normal sensory and motor function in all limbs. Deep tendon reflexes were 2+ throughout. Radiologic evaluation revealed the presence of metastases in the lumbar vertebrae and lung. Laboratory results consisted of the following:

Laboratory Results

Na=121 mEq/L; K=4.1 mEq/L; Cl=89 mEq/L; TCO₂=23 mEq/L;
 BUN=7 mg/dL; Creatinine=0.6 mg/dL; Glucose=98 mg/dL;
 Ca=9.8 mg/dL; Albumin=3.1 g/dL; Uric Acid=1.4 mg/dL;
 Plasma Osmolality=250 mOsm/kg; TSH=3.1 μIU/mL;
 AM Cortisol=25 μg/dL; Urine Osmolality=560 mOsm/kg;
 Urine Na=97 mEq/L; Urine K=45 mEq/L

Nephrology was consulted to address hyponatremia prior to administration of chemotherapy. The patient was diagnosed with hypotonic hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), likely multi-

factorial from pain, nausea, and metastatic lung involvement. Fluid restriction is the mainstay of therapy for patients with SIADH, however this patient's urine osmolality was greater than 500 mOsm/kg, and her urine electrolyte-to-plasma ratio ($([UNa + UK]/PNa)$) was greater than 1, suggesting that fluid restriction alone was not going to improve PNa.^{14,15} Therefore, a decision was made to start urea 15 grams orally, twice a day. The patient was maintained on 1.5 L/day fluid restriction while on urea. Plasma sodium concentration normalized over three days (Table 1).

Table 1. Evolution of Blood and Urine Parameters Before and During Treatment With Urea

Laboratory Parameters	Before Urea	During Urea			
		Day 1	Day 2	Day 3	Day 4
PNa (mEq/L)	121	125	131	135	137
BUN (mg/dL)	7	15	23	24	25
Cr (mg/dL)	0.6	0.6	0.5	0.6	0.6
UOsm (mOsm/kg)	560	—	—	600	—
UNa (mEq/L)	97	—	—	43	—
UK (mEq/L)	45	—	—	29	—
UOP (L/day)	1.2	—	—	1.6	—
CeH ₂ O (L/day)	-0.21	—	—	+0.75	—

PNa = plasma sodium concentration; BUN = blood urea nitrogen concentration; Cr = plasma creatinine concentration; UOsm = urine osmolality; UNa = urine sodium concentration; UK = urine potassium concentration; UOP = daily urine output; CeH₂O = electrolyte-free water clearance.

Mechanism of Action of Urea

Urea is considered an ineffective osmole because it crosses cell membranes, but in the kidneys urea can work as an effective osmole inducing osmotic diuresis. To better understand how urea qualitatively works as an osmotic diuretic, we should first briefly review the renal handling of urea.¹⁶⁻¹⁸ Urea is freely filtered by the glomerulus. As water is reabsorbed in the proximal tubule (PT), the concentration of luminal urea rises, creating a chemical gradient for about 50% of the luminal urea to be passively reabsorbed in the last portion of the PT. Some urea also is secreted into the lumen of the thin limbs of the loop of Henle (tLH). UTA2 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 (TALH) to the outer medullary collecting duct (OMCD). The inner medullary collecting duct (IMCD) is permeable to urea only in the presence of vasopressin, and urea reabsorbed here contributes to approximately 50% of the hypertonic medullary osmotic gradient.¹⁹ Urea enters IMCD cells via urea transporters UTA1 in the apical cell membrane, and exits the cell via UTA3 in the basolateral cell membrane. Part of the urea deposited in the medullary interstitium is secreted again in the TALH, the so-called urea recycling mechanism. The connecting tubule (CNT), the cortical collecting duct (CCD), and the OMCD are permeable to water, therefore these segments are the likely sites where urea exerts its main osmotic effects, especially when luminal urea concentration is high. Rates of urea excretion increase during high-protein diets, post-ATN and post-obstructive diuresis, and oral urea administration.² Under such circumstances, urea becomes an effective osmole in the lumen of water-impermeable nephron segments and obligates water excretion. The IMCD segment might also be a site of urea action as UTA1 can undergo downregulation when the luminal concentration of urea is high, increasing the osmotic diuretic effect of urea.²⁰ To appreciate how urea quantitatively works, we should also briefly review the dependence of free water clearance on daily urine solute excretion.²¹

Urine osmolality is the ratio between daily urine solute excretion and daily urine volume as shown in equation (1):

$$\text{UOsm} = \text{USE}/V \dots (1)$$

Where UOsm = urine osmolality (in mOsm/L); USE = daily urine solute excretion (in mOsm/day); V = daily urine volume (in L/day).

Reorganizing the terms of equation (1) we then have:

$$V = \text{USE}/\text{UOsm} \dots (2)$$

From equation (2) we can infer that daily urine volume (and therefore free water clearance) depends on daily urine solute excretion.²¹ This is the principle behind the hyponatremia from beer potomania and tea-and-toast diet, as well as the polyuria induced by glycosuria or other osmotic agents.²²

Under normal circumstances, we are in solute balance, which means that the daily solute intake equals the daily urine solute excretion. We can illustrate the effects of urea on water balance by using three examples:²³

1. A healthy individual who ingests 700 mOsm of solute and drinks 2 liters of water per day. The kidneys adjust urine osmolality based on solute and water intake to maintain water homeostasis:

Replacing values in equation (1) we have:

$$\text{UOsm} = \frac{700 \text{ mOsm/day}}{2 \text{ L/day}} = 350 \text{ mOsm/L}$$

Replacing values in equation (2) we now have:

$$V = \frac{700 \text{ mOsm/day}}{350 \text{ mOsm/L}} = 2 \text{ L/day}$$

Net water gain = Water intake - Water excretion

$$\text{Net water gain} = 2 \text{ L/day} - 2 \text{ L/day} = 0 \text{ (i.e., water balance)}$$

2. A patient with SIADH who ingests 700 mOsm of solute and drinks 2 liters of water per day. The kidneys are not able to adjust urine osmolality based on solute and water intake in SIADH. On the contrary, SIADH is characterized by a high and "fixed" urine osmolality (in our example we use a urine osmolality of 500 mOsm/L):

Replacing values in equation (2) we have:

$$V = \frac{700 \text{ mOsm/day}}{500 \text{ mOsm/L}} = 1.4 \text{ L/day}$$

Net water gain = 2 L/day - 1.4 L/day = +0.6 L/day
(water excess resulting in hyponatremia)

3. A patient with SIADH who ingests 700 mOsm of solute and drinks 2 liters of water per day but also is treated with urea 15 g orally twice daily (i.e., molecular weight of urea is 60 g/mol, 30 g = 500 mmol of urea daily). The kidneys are still not able to adjust urine osmolality because urine osmolality remains fixed, but daily solute intake has now increased due to the ingestion of urea.

Replacing values in equation (2) we have:

$$V = \frac{700 \text{ mOsm/day (diet)} + 500 \text{ mOsm/day (urea)}}{500 \text{ mOsm/L}}$$

$$V = \frac{1200 \text{ mOsm/day}}{500 \text{ mOsm/L}} = 2.4 \text{ L/day}$$

Net water gain = 2 L/day - 2.4 L/day = -0.4 L/day
(water deficit resulting in correction of hyponatremia)

Besides a dilutional component, the mechanism of hyponatremia in SIADH also involves renal sodium loss as a compensation for the mild volume expansion that occurs in this syndrome.²⁴ In an animal model, urea improved hyponatremia in SIADH by decreasing the associated compensatory natriuresis (perhaps by increasing sodium reabsorption in the thin ascending limb of the loop of Henle).²⁵

Efficacy of Urea

There are no randomized clinical trials that have investigated the efficacy of urea in the treatment of hyponatremia. The evidence for the efficacy of urea mostly comes from retrospective studies and case series in various patient populations (Table 2).

Decaux et al. reported seven patients with hyponatremia from chronic SIADH (mean PNa 115.6 mEq/L) who could not tolerate fluid restriction and were given oral urea in a dose of 30 or 60 g/day.²⁶ Despite lack of fluid restriction, urea corrected PNa in all of the patients (mean PNa during treatment was 136 mEq/L). Those patients with higher fluid intake required higher doses of urea. No major side effects were reported after up to nine months of treatment.

The efficacy of urea in critically ill patients has also been reported. Decaux et al analyzed the charts of patients in the intensive care unit who were treated with urea for hyponatremia while receiving isotonic or hypotonic intravenous fluids.²⁷ They found that in 50 consecutive patients with moderate hyponatremia (PNa between 120 to 134 mEq/L), urea increased PNa in all patients (Δ PNa in 2 days was 7 ± 4 mEq/L; $P < 0.001$). The mean dose of oral urea for this group of patients was 46 ± 25 g/day, and most patients received urea by feeding tube. In a second group of 35 patients with severe hyponatremia (PNa ≤ 115 mEq/L) associated with neurological symptoms in the majority of patients, the investigators found that urea increased PNa from 111 ± 3 mEq/L to 122 ± 4 mEq/L in one day ($P < 0.001$), improving the neurological symptoms of affected patients. Twelve patients in this group with severe hyponatremia increased PNa over 12 mEq/L during the first 24 hours, and two of them required re-lowering of PNa, but no cases of osmotic demyelination syndrome (ODS) developed.

Hyponatremia that occurs in patients with subarachnoid hemorrhage from ruptured intracranial aneurysm is usually caused by SIADH, with glucocorticoid deficiency being the

second most common cause; cerebral salt wasting syndrome is rare in these patients.²⁸ Therefore, urea might play a role in these patients where cerebral edema is usually present and fluid restriction is a concern due to the potential risk of vasospasm.²⁹ As a matter of fact, vasospasm is prevented in these patients by volume expansion with isotonic saline but with the added risk of worsening hyponatremia from SIADH due to the desalination phenomenon.³⁰ The concomitant use of urea with isotonic saline has prevented this problem. Pierrakos et al performed a retrospective review of 42 patients with nontraumatic subarachnoid hemorrhage who developed hyponatremia (PNa before urea 127 ± 2 mEq/L) from SIADH treated with oral urea³¹ after failing volume expansion with isotonic saline. Urea was given for a mean of 5 days at a mean dose of 50 g/day. Most patients received urea via feeding tube. Hyponatremia was reversed in all patients, with PNa returning to 135 mEq/L after a median time of 3 days. Reeder et al reported a similar successful experience in neurosurgical patients from various etiologies who received intravenous urea and isotonic saline for hyponatremia.³²

Psychogenic polydipsia has been traditionally considered a pure dilutional hyponatremia from excessive water intake. However, there is evidence suggesting that factors other than excessive water intake might play a role.^{33,34} Urea has also been used in patients with psychogenic polydipsia where fluid restriction was found to be difficult to adhere to.^{35,36}

Case reports of the successful use of urea in hyponatremic patients with heart failure and cirrhosis have been also reported.³⁷⁻³⁹

Urea has also been shown to be effective in some situations where VRAs do not work. This is the case of the nephrogenic syndrome of inappropriate antidiuresis (NSIAD), a genetic disorder caused by activating mutations in the vasopressin 2 receptor, where urea has been used successfully.⁴⁰

Table 2. Populations of Patients With Hyponatremia Where Urea Has Been Successfully Used

- SIADH
- NSIAD
- Critically ill patients
- Nontraumatic subarachnoid hemorrhage
- Psychogenic polydipsia
- Heart failure

Advantages of Urea

Hyponatremia has been associated with various degrees of cerebral edema, especially in neurosurgical patients. Urea is considered an ineffective osmole because it crosses muscle cell membranes very rapidly; urea penetrates brain capillaries 10 times more slowly than in muscle, becoming at least a partly effective osmole under these circumstances.^{41,42} Oral urea administration can result in a rapid increase in urea levels, creating an osmotic gradient across the blood-brain barrier that causes water to exit out of the brain, improving cerebral edema.⁴²

Another advantage of urea is that it seems to be protective against ODS when overcorrection of hyponatremia occurs. This might be the reason behind why ODS is an uncommon occurrence in chronic hemodialysis patients.⁴³ Induction of azotemia in rats with the subsequent development of hyponatremia and posterior PNa overcorrection was found to be protective of ODS.⁴⁴ Administration of urea to hyponatremic rats after PNa overcorrection has also been shown to protect against ODS.⁴⁵⁻⁴⁸ Gankam Kengne et al. studied hyponatremic rats whose PNa was overcorrected using urea, lixivaptan, or hypertonic saline.⁴⁸ All animals developed a similar degree of PNa overcorrection. Fewer animals developed ODS in the urea group, and when they did, their neurologic manifestations were less pronounced compared to the animals in the lixivaptan and hypertonic saline groups. Also, the mortality in the urea group was significantly less compared to the other two groups (27% for urea, 65% for lixivaptan, and 76% for hypertonic saline). The pathogenesis of ODS remains unclear, but demyelination, microglial activation, and astrocyte loss are considered histological features. In this study, the brains of rats in the urea group showed less demyelination, less microglial activation, and less astrocyte loss compared to the brains of rats treated with the other therapies. The explanation of the protective mechanism of urea during hyponatremia overcorrection might lie in the way the brain adapts to hyponatremia and its correction.^{49,50} After hyponatremia develops, water moves into the brain along osmotic gradients, producing brain edema. Astrocytes have an important role in brain water regulation and selectively swell after hypotonic stress, while neurons do not. Immediate adaptation to brain swelling includes movement of fluid from astrocytes into the cerebrospinal fluid driven by a hydrostatic pressure gradient created by increased intracranial pressure. However, this is a limited adaptive mechanism. The main way

astrocytes fully adapt to swelling is by extruding solutes in an effort to decrease their intracellular fluid (ICF) osmolality and stop water movement, a process known as regulatory volume decrease (RVD). Initially, astrocytes lose electrolytes, mainly K^+ and Cl^- ions. This process peaks at 3 hours. However, the ongoing use of electrolytes in cellular osmoregulation can cause disturbances in ion gradients across cell membranes affecting cellular function, so this process is limited. Cells then start extruding organic osmolytes, such as glycerophosphorylcholine, phosphocreatine, creatine, glutamate, glutamine, taurine, and myoinositol. Full adaptation occurs by 48 to 72 hours. On the other side, during correction of chronic hyponatremia, ECF osmolality increases, and astrocytes then employ a reverse process known as regulatory volume increase (RVI). During RVI, astrocytes uptake osmolytes to increase ICF osmolality and prevent cell shrinkage. It appears that oligodendrocytes are especially sensitive to death by volume loss, which could trigger the development of ODS.^{51,52} Apparently urea is beneficial because it facilitates RVI during correction of hyponatremia by causing a rapid uptake of myo-inositol and other organic osmoles into astrocytes.⁵³ Overcorrection of hyponatremia can also result in hyperionization of astrocytes, causing proteostasis failure (i.e., protein misfolding) and contributing to astrocyte death and destruction of astrocyte oligodendrocyte gap junctions, which are features of ODS.^{48,54,55} Urea might be protective against ODS by promoting folding of proteins and a proteostasis-friendly environment within astrocytes during hyponatremia overcorrection.⁵⁴

Studies Comparing the Efficacy of Urea to Other Therapies

Soupart et al. studied the efficacy, safety, and tolerability of urea compared to VRAs in 13 patients with chronic hyponatremia.⁵⁶ Patients were treated with VRAs for 1 year. PNa increased from 125 ± 3 mEq/L to 135 ± 3 mEq/L by the end of the year. VRAs were then discontinued, and patients were allowed to become hyponatremic again. Urea was then introduced and maintained for a year. PNa normalized with urea (mean final PNa was 135 ± 2 mEq/L). The patients tolerated urea well without significant side effects.

Drawbacks of Urea

The use of urea has been limited because of its bitter taste. However, the U.S. formulation of urea has a sweet citrus flavor, which makes it more tolerable. The author of this review has personally tried this urea formulation and found the taste very acceptable. Urea is generally safe. Common side effects of urea include headaches, and nausea when administered rapidly via feeding tube. BUN and urine osmolality levels are expected to increase with urea use, and urine sodium concentration decreases.¹²

Indications and Dosing of Urea

Urea is indicated in the treatment of hypotonic hyponatremia without severe symptoms (where hypertonic saline is still the treatment of choice) resulting from the following conditions:

- SIADH:** The main indication for urea is to treat the hyponatremia resulting from SIADH.^{12,26,57} The 2014 European clinical practice guidelines on the diagnosis and treatment of hyponatremia recommend the use of urea (or alternatively a combination of low-dose loop diuretics and salt tablets) as a second-line therapy in patients with moderate or profound hyponatremia from SIADH.⁵⁸ The same guidelines advise against the use of VRAs for this purpose. Urea should be used after fluid restriction alone is expected to fail, has failed, or is not tolerated. However, patients on urea should still limit their fluid intake to 1.5 to 2 L/day. The recommended dose of urea is 0.25 to 0.5 g/kg/day or 15 to 30 g/day. The higher the urine osmolality, the higher the dose of urea required. Professor Guy Decaux, a world expert in hyponatremia and the use of urea, recommends the following urea doses based on initial urine osmolality:⁵⁹

UOsm \approx 300 to 500 mOsm/kg: Urea 15 g orally daily

UOsm \approx 500 to 600 mOsm/kg: Urea 15 g orally
twice a day (30 g/day)

- Heart Failure:** Urea has been used successfully in hyponatremia for heart failure.⁶⁰ The dosing is similar to that of SIADH, but diuretics should be maintained. Urea should be initiated only if BUN is less than 28 to 38 mg/dL.⁵⁹
- Liver Cirrhosis:** Urea is rarely used in hyponatremia from cirrhosis.^{38,39} The main concern is that urea metabolism into ammonium by colonic ureases can trigger hepatic encephalopathy.⁶¹

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The Renal-Electrolyte Division is devoted to clinical care and academic excellence, and training the next generation of nephrologists. Our multidisciplinary approach provides the highest quality care for patients with complex kidney and electrolyte disorders.

- Inpatient services at UPMC Presbyterian tend to patients awaiting or who have received kidney transplants, and the on-site dialysis center performs nearly 10,000 dialysis treatments a year in various ICU settings.
- Outpatient services are provided at our specialized kidney and multidisciplinary clinics treating a variety of kidney and hypertensive disorders.
- The Pittsburgh Center for Kidney Research, one of seven nationwide NIDDK-supported George M. O'Brien Kidney Research Core Centers, supports more than 140 investigators and provides funding for pilot projects.

ADDRESS CORRESPONDENCE TO:

**Helbert Rondon-Berrios, MD,
FACP, FASN**

*Assistant Professor of Medicine,
University of Pittsburgh School of
Medicine; Associate Program Director,
Nephrology Fellowship Training
Program, UPMC
Renal-Electrolyte Division*

A915 Scaife Hall
3550 Terrace St.
Pittsburgh, PA 15261
Phone: 412-647-3120
Fax: 412-647-6220
Email: rondonberriosh@upmc.edu

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