What Is the Role of Vaptans in Routine Clinical Nephrology?

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Hyponatremia is the most common electrolyte disorder encountered in hospitalized patients, and both community- and hospital-associated hyponatremia are associated with in-hospital mortality and heightened resource consumption (1). As described by Wald et al. (1) in their evaluation of close to 100,000 hospitalizations during their 7-year study, it is not known whether hyponatremia is a marker of the severity of the underlying condition(s) or a direct contributor to the adverse outcomes observed. With the advent of vasopressin V2 receptor antagonists (termed vaptans) to treat hyponatremic patients, this important clinical question could be tested. The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) studies have demonstrated that tolvaptan, an oral vasopressin V2 receptor antagonist, was effective in increasing serum sodium concentration at day 4 and day 30 (2). As a follow-up, 111 patients with hyponatremia received tolvaptan for a mean of 701 days, with maintenance of the increased serum sodium (3). These important studies included mildly symptomatic patients, but patients with a serum sodium <120 mmol/L in association with neurologic impairment were excluded. Vaptans are expensive drugs and their use in symptomatic patients has not been assessed. Vaptans seem to be as safe as urea according to Soupart et al. (7) in the present issue of CJASN, and urea is not expensive at all. The authors are suggesting that both vaptans and urea should be tested to decrease adverse outcomes in symptomatic and nonseverely symptomatic hyponatremic patients. Soupart et al. and Decaux et al. from two different hospitals in Belgium have been promoting the use of oral urea to treat patients with hyponatremia (4–7).

Urea Is a Nonspecific Treatment for Hyponatremia: It Will “Drag” Excess Water in Urine because of Simple Math (Box 1)

If you assume a maximally diluted urine of ~60 mOsm/kg and a solute excretion of an adult male of 900 mOsm/d, then V = 900/60 = 15 L/d. A urine osmolality of 60 corresponds to a maximal ability to dilute urine. In this condition, the antidiuretic hormone, vasopressin, is suppressed and the vasopressin V2 receptor on the basolateral side of the principal cells of the collecting duct is not activated; therefore, there is no aquaporin 2 expressed on the luminal side to transport water transcellularly and to be retrieved to the renal vasa recta. By contrast, if vasopressin is not suppressed by hypotonicity as occurs in the syndrome of inappropriate antidiuretic hormone secretion (syndrome of inappropriate antidiuretic hormone secretion [SIADH]), heart failure, and cirrhosis, urinary osmolality is higher than plasma osmolality and you have now to think quantitatively about the physiology of urine concentration and the effect of oral urea: (Boxes 2 and 3).

You can also use different numbers: if urinary osmolality is fixed at 800 mOsm/kg and if daily intake is 700 mmol + 500 mmol of urea, the urinary daily volumes will be 1200/800 = 1.5 L.

Urea Is Not Expensive and Has a Bitter Taste

“Medicinal urea” 30 g × 1 month will be less than $50 here in Montreal, and this low cost is mainly related not to urea per se (<$0.50/30 g) but to the 15 g/30 g doses that have to be weighed and placed into small packages. This could be simplified by prescribing teaspoonfuls of a larger bottle like nephrologists do for Kayexalate and the chronic treatment of hyperkalemia. Urea has “an unpleasant taste” (7). I decided to test it myself. I mixed 15 g in 120 ml of cold orange juice: it does not smell of anything but the bitterness is strong. I used the full 300 ml orange juice bottle to dilute it completely to decrease the bitterness; if I would have been on water restriction, these 300 ml would have decreased my allowed daily water intake. Urea is included in the list of bitter compounds reviewed by Meyerhof et al. (8).

Taste receptor cells are assembled into taste buds that are distributed across different papillae of the tongue and palate epithelium (9). Chandrashekar et al. (9) provided localization of these bitter taste receptors: circumvallate papillae at the very back of the tongue and foliate papillae at the posterior lateral edge of the tongue contain thousands for the former and hundreds for the latter taste buds. While ingesting urea, I had the distinct perception of bitterness in

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<td>( V = ) urinary volume Liter/day = ( \frac{\text{solute excretion (mOsm/day)}}{\text{urinary osmolality (mOsm/Liter)}} )</td>
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the back lateral part of my tongue; I read the article by Chandrashekar et al. afterward.

The Vaptans to Treat Euvolemic or Hypervolemic Hyponatremia

Vaptans are nonpeptide vasopressin V2 receptor antagonists, and they look like vasopressin; therefore, they are able to bind reversibly to the vasopressin V2 receptor and to induce a conformation change of the vasopressin V2 receptor that will not allow its interaction with the G-binding protein. This “blocked” conformation will not allow GDP release from Gs-α: the receptor–G protein complex will not be activated. As a consequence, there will be no activation of adenylyl cyclase, no generation of cyclic-AMP, and no insertion of AQP2 water channels in the luminal membrane of the principal cells of the collecting ducts (Figure 1). We suppose that it is working like this, but a seven transmembrane receptor image in embrace with a G protein and the interface of the two Gs-α subdomains forming the nucleotide binding pocket has only been obtained recently for the β-adrenergic receptor (10) and not for the vasopressin V2 receptor. This mechanism of action indicates that the vaptans are specific treatment for hyponatremic states with high vasopressin plasma levels including patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH: euvolemic hyponatremia), liver cirrhosis with ascites and edema, and severe heart failure (hypervolemic hyponatremia). Conivaptan for intravenous use and tolvaptan for oral administration are now on the market for the treatment of euvolemic (Europe) or euvolemic and hypervolemic (United States); in Canada, only tovaptan is on the market for both euvolemic and hypervolemic hyponatremic states. It is an expensive medication, US $244/d, extensively commented on by Gross et al., long time warriors in the hyponatremia field (11). In a recent study based on SALT-1 and-2 trials, tolvaptan use was found to be associated with a shorter hospital stay compared with placebo among patients with SIADH: when the drug cost for 4 days of inpatient tolvaptan therapy was included, tolvaptan was associated with a mean hospital cost reduction of $694 per admission in the United States (12). The meta-analysis of 15 randomized controlled trials comparing vaptans with placebo, no treatment, and/or fluid restriction clearly showed an improvement or normalization of serum sodium without major side effects (13). There were six trials for tolvaptan, four trials for satavaptan, three trials for conivaptan, and two trials for lixivaptan. In the tolvaptan trial, plasma sodium increased by 4.8–3.5 mEq/L at day 4 and from 7.4 to 4.2 mEq/L at day 30 for all patients with a plasma sodium <135 mEq/L (213 patients on tolvaptan and 203 patients on placebo) (2). These patients had little or no neurologic symptoms attributed to hyponatremia, and the important group of patients with a serum sodium <120 mEq/L with neurologic impairment was excluded from these studies because it was felt that they would not benefit from the trial if they were to enter the placebo group. In all the patients tested there was no report of osmotic demyelination syndrome (14). A strategy for the controlled correction of profound hyponatremia has been proposed by Sterns et al. (15) to help seasoned nephrologists treating “double digit hyponatremia” and afraid of iatrogenic injury from overcorrection. Sterns et al. underlined the high risk of unintentional overcorrection if the cause of water retention is reversible and provided teaching points to treat profound hyponatremia and correction goals for severe chronic hyponatremia; I am using his teaching points and correction goals and I am trying to enforce them not only to medical students but also to nurses when I am writing chart orders related to the treatment of real patients, especially late in the evening in the emergency room or in the intensive care unit.
Vaptan Therapy Is Ineffective but Urea Is Effective in the Vasopressin-Independent Form of Inappropriate Antidiuresis caused by Constitutive Activation of Vasopressin V2 Receptors

Loss-of function mutations in the type 2 vasopressin receptor (AVPR2) lead to nephrogenic diabetes insipidus, with affected patients producing large amounts of dilute urine (16). Conversely, gain-of-function mutations in AVPR2 lead to nephrogenic syndrome of inappropriate antidiuresis (NSIAD), the mirror image of nephrogenic diabetes insipidus, and affected patients produce persistently concentrated urine despite low or absent levels of vasopressin. In all previously described NSIAD cases, substitution of arginine-137 by either a cysteine or a leucine (R137C/L) induces the spontaneous activation of the vasopressin V2 receptor that could not be reversed by vaptans (17). The inability of vaptans to decrease urine osmolality in NSIAD might be related to the constitutive desensitization and endocytosis of the receptor bearing the mutations R137L/C. Huang et al. (18) have reported that, after administration of 30%–50% oral urea solutions, serum sodium could be normalized in these children.

Vaptans for 1 Year followed by Urea for 2 Years in 12 Patients with SIADH

Soupart et al. (7) demonstrated in this issue of CJASN that hyponatremia increased from 125 to 135 mEq/L under...
tolvaptan or satavaptan. After discontinuation of vaptans, hyponatremia recurred in the 12 participants, but urea treatment improved plasma sodium to the same 135 mEq/L value. One patient on vaptan stopped his medication because of excessive thirst, and one episode of hyponatremia (155 mEq/L) was observed in an 89-year-old man with pneumonia. The authors have had considerable previous experience with acute (4) and long-term urea treatment (19), but this is the first observation of long-term administration of vaptans followed by urea. Given the similar efficacy and tolerance, Soupart et al. propose that prospective trials evaluating morbidity, mortality, and quality of life should be done.

**Hyponatremia Could Be Better Recognized, Evaluated, and Treated**

I hope that all the clinical evaluations, pathophysiological evaluations, and treatment of hyponatremic cases that have been found to be suboptimal in large hospital settings (20) could benefit from the clinical and therapeutic approaches provided by the vaptan studies: we know that hypertonic saline) and to fear overtreatment and osmotic neurologic symptoms associated with hyponatremia (with their limitations and the absolute necessity to treat severe euvolemic and hypervolemic hyponatremic patients knowing their limitations and the absolute necessity to treat severe neurologic symptoms associated with hyponatremia (with hypertonic saline) and to fear overtreatment and osmotic demyelination.

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**References**


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See related article, “Efficacy and Tolerance of Urea Compared with Vaptans for Long-Term Treatment of Patients with SIADH,” on pages 742–747.