When Is It Appropriate to Use Vasopressin Receptor Antagonists?

Ruediger W. Lehrich and Arthur Greenberg
Department of Medicine, Division of Nephrology, Duke University Medical Center, Durham, North Carolina

ABSTRACT
Hyponatremia is a common and challenging disorder. The mainstays of treatment until recently were water restriction and hypertonic saline. The first nonpeptide vasopressin receptor antagonist (VRA) is now approved by the US Food and Drug Administration for use in patients with euvolemic and hypervolemic hyponatremia. VRA induce urinary dilution with an aquarexis that leads to an increase in serum sodium concentration. In patients with heart failure, VRA modestly improve congestive symptoms but have no effect on short- or long-term mortality. Long-term effects have not been extensively studied, but serious adverse effects of VRA are rare, and the rate of rise in serum sodium that they produce seems unlikely to lead to osmotic demyelination. Beneficial effects beyond changing serum tonicity and alternative uses, such as in polycystic kidney disease, need further exploration. This commentary discusses the current and potential indications for use of VRA.


DEVELOPMENT OF VRA
Although peptide antagonists of vasopressin receptors showed promise in animal models in the 1970s, they had partial agonist effect in humans and further development was abandoned. Subsequently, nonpeptide receptor antagonists were identified and used successfully for the first time in humans in the early 1990s. In December 2005, the first such compound, conivaptan, a combined vasopressin 1a receptor (V1aR) and V2R antagonist, was approved by the Food and Drug Administration for use in euvolemic hyponatremia. An indication for hypervolemic hyponatremia was granted more recently. Although effective in an oral formulation, conivaptan is a potent CYP3A4 inhibitor. To protect against the possibility of important drug interactions, its approval was limited to short-term, parenteral use. Three other agents, tolvaptan, lixivaptan, and sat-
avaptan, each a selective V2R antagonist (V2RA), are in various stages of development for commercial use. Tolvaptan is the furthest along, and the highest quality data are available for this congener. Characteristics of these agents are summarized in Table 2.

### USE OF VRA IN HYponatremia

Decaux demonstrated in 2001 that oral administration of conivaptan in two patients with well-established, longstanding syndrome of inappropriate antidiuretic hormone secretion led to a rise in sodium with a concomitant decrease in body weight. This effect was sustained, reversing only after discontinuation of conivaptan (Figure 1). In a placebo-controlled trial of conivaptan administered intravenously to patients with hypervolemic or euvolemic hyponatremia, sodium rose approximately 8 mEq/L during the first 24 h in the group that received active drug versus 0.5 mEq/L in the group that was treated with fluid restriction alone. Electrolyte-free water excretion was higher and minimum urinary osmolality lower in the active drug group.

Schrier et al. conducted two identical trials to test the efficacy of oral tolvaptan in patients with euvolemic and hypervolemic hyponatremia. Suitably named SALT-1 and SALT-2 for Study of Ascending Levels of Tolvaptan in Hyponatremia, an American and international cohort of 448 patients was randomly assigned to tolvaptan or placebo. In SALT-1, sodium rose from 128.5 mmol/L at baseline to 133.9 mmol/L on day 4 and 135.7 ± 5.0 mmol/L on day 30 in patients who received active drug but only from 128.7 mmol/L to 129.7 ± 4.9 and 131.0 ± 6.2 mmol/L, respectively, in the placebo group. The rise in sodium exceeded 12 mmol/L per 24 h in only four of the 225 patients who received tolvaptan. Dry mouth and increased thirst and urination were more frequent in the treatment group, and the remainder of adverse effects was similar in both groups. Serious adverse effects potentially a result of tolvaptan treatment occurred in eight patients: Hypotension, dizziness, syncope, acute renal failure, and hypernatremia. This study clearly demonstrated that orally administered tolvaptan effectively and safely treats euvolemic and hypervolemic hyponatremia.

In smaller studies, the selective V2RA

---

**Table 1. Vasopressin receptors, localization, and effects**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Localization</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1a</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction, myocardial hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Hepatocytes</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Myometrium</td>
<td>Uterine contraction</td>
</tr>
<tr>
<td>V1b (V3)</td>
<td>Anterior pituitary</td>
<td>ACTH release</td>
</tr>
<tr>
<td>V2</td>
<td>Basolateral membrane, collecting tubule</td>
<td>Insertion of AQP2 water channels into apical membrane</td>
</tr>
<tr>
<td></td>
<td>Vascular endothelium</td>
<td>Induction of AQP2 synthesis</td>
</tr>
<tr>
<td></td>
<td>Vascular smooth muscle</td>
<td>vWF and factor 8 release</td>
</tr>
</tbody>
</table>

aAQP2, aquaporin 2; vWF, von Willebrand factor.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conivaptan</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>V1a and V2</td>
<td>V2</td>
</tr>
<tr>
<td>route of administration</td>
<td>Intravenous</td>
<td>Oral</td>
</tr>
<tr>
<td>urine osmolarity</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>free water clearance</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Na⁺ excretion/24 h</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

- ADPKD, autosomal dominant polycystic kidney disease; CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
- Like tolvaptan, lixivaptan and satavaptan are selective V2RA with similar characteristics and anticipated indications.
- Conivaptan is effective when administered orally, but only the parenteral formulation is approved by the Food and Drug Administration.
- Refers to chronic and non–life-threatening hyponatremia.
- Food and Drug Administration–approved indication.

---

**Table 2. Characteristics and clinical indications for the combined V1a/V2 receptor blocker conivaptan and the selective V2 receptor blockers tolvaptan, lixivaptan, and satavaptan**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conivaptan</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>characteristics</td>
<td>V1a and V2</td>
<td>V2</td>
</tr>
<tr>
<td>route of administration</td>
<td>Intravenous</td>
<td>Oral</td>
</tr>
<tr>
<td>urine osmolarity</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>free water clearance</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Na⁺ excretion/24 h</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

- ADPKD, autosomal dominant polycystic kidney disease; CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
- Like tolvaptan, lixivaptan and satavaptan are selective V2RA with similar characteristics and anticipated indications.
- Conivaptan is effective when administered orally, but only the parenteral formulation is approved by the Food and Drug Administration.
- Refers to chronic and non–life-threatening hyponatremia.
- Food and Drug Administration–approved indication.
rixivaptan and satavaptan also were more effective than placebo in treating euvo-
lemic or hypervolemic hyponatremia. In all of the reported trials, orthostatic hypo-
tension, dizziness, or other symptoms of volume depletion were noted, and adjust-
ment of dosing was often required to mitigate this effect of aquaresis. The effect of
the drugs to increase thirst has the potential to blunt their efficacy.10–12

USE OF VRA IN HEART FAILURE

Levels of catecholamines, angiotensin, and aldosterone all are increased in CHF, and
blockade of their effects has been repeatedly shown to improve survival.13 The hy-
pothesis that outcome could be improved by interference with the maladaptive in-
crease in AVP observed in patients with heart failure was tested in the Efficacy of
Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVER-
EST) trials.14,15 In two identical, short-term, multicenter, international trials, pa-
tients who were hospitalized with decompensated CHF were given either tolva-
ptan or placebo within 48 h of admission. A total of 2072 patients received
tolvaptan, which was superior to placebo in achieving the primary end point, a com-
posite of patient-assessed global clinical status and body weight at 7 d or at dis-
charge; however, the observed effect was modest and entirely driven by the differ-
ence in weight loss from aquaresis, which was a mean of 1.82 kg in the tolvaptan
group and 0.85 kg in the placebo group. Serum sodium during the administration
of tolvaptan rose by 2 mmol/L at discharge. There were some improvements in sec-
ondary end points, namely dyspnea and edema in the tolvaptan treatment group.
Dry mouth, thirst, and polyuria were significantly more common in the tolvaptan
group, although the incidence of serious adverse effects was similar. In long-term
follow-up conducted for up to 2 yr (median 9.9 mo), neither a mortality benefit
nor a reduction in heart failure hospitalizations was observed with tolvaptan. Taken
together, these trials indicate that tolvaptan can improve some CHF symptoms in the
short term, but it does not improve mor-
tality in the long term. Importantly, the
drug was well tolerated and safe. One possible conclusion to be drawn from EVER-
EST is that elevated AVP levels are not ac-
tually harmful in CHF; however, it is also
possible that no benefit was observed be-
cause the fixed dosage of tolvaptan that was
used was too low or because tolvaptan’s se-
lective blockade of the V2R left the poten-
tially more deleterious vasoconstrictor
V1aR effect unopposed or even augmented
as AVP levels rose with treatment.

USE OF VRA IN POLYCYSTIC
KIDNEY DISEASE

In patients with autosomal dominant polycystic kidney disease (ADPKD), un-
opposed cAMP promotes cystogenesis by stimulating fluid secretion and cellu-
lar proliferation in evolving cysts.16 V2R act through cAMP to mediate their intra-
cellular effect. It was hypothesized and confirmed in animal models that V2RA
lower cAMP levels and retard cyst develop-
ment.17,18 A phase IIb trial in humans with ADPKD and normal renal function
to determine the effect of increasing dosages of tolvaptan was recently com-
pleted.19 A phase III trial studying the disease progression of ADPKD in pa-
tients who are receiving tolvaptan is on-
going.20

WHEN AND HOW SHOULD
VASOPRESSIN ANTAGONISTS BE
USED?

Euvolemic and Hypervolemic
Hyponatremia

The controversy about how rapidly hy-
ponatremia should be corrected has been largely resolved.4 The key point is that

Figure 1. Patient who had chronic hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion and
underwent treatment with oral conivaptan, water restriction, and urea. Changes in body weight (○) and changes in serum sodium (●)
are depicted. BID, twice a day. Reprinted from Decaux,7 with permission.
acute hyponatremia and chronic hyponatremia are different and must be managed with different goals in mind. In acute, severe hyponatremia, the brain has had little time to compensate for the fall in serum sodium by shedding intracellular osmoles. Cerebral edema from water uptake may be present or imminent, and severe alterations in sensorium with a high risk for seizures or other adverse events such as noncardiac pulmonary edema are present. Here, the risk of persistent marked hyponatremia far exceeds any risk from correction of serum sodium. Therapy with an agent that is certain to raise sodium is essential. Conversely, in chronic hyponatremia, the brain has had time to adjust. Intracellular electrolytes and organic osmoles have been shed, cerebral edema is unlikely, and symptoms are bothersome but typically not life-threatening. Treatment regimens must take into account the risk for permanent neurologic sequelae from osmotic demyelination caused by overly rapid correction. Therapy should be deliberate, with the goal of correcting sodium by no more than 12 mmol/L in the first 24 h and no more than a total of 18 mmol/L in the first 48 h. 

Although V2RA should work in acute severe hyponatremia, no published data address this assertion; all of the studies testing V2RA in patients with hyponatremia were randomized, placebo-controlled trials that of necessity excluded this patient population that could not ethically have been randomly assigned to receive placebo. V2RA do begin to raise sodium within 1 to 2 h. Even so, at present, hypertonic saline either alone or with a loop diuretic remains the proven treatment for acute, severe, life-threatening hyponatremia. Hypertonic saline is far from ideal because its use can lead readily to volume overload. A combination of hypertonic saline with a simultaneously administered V2RA makes much sense, but firm recommendations await data. With this combination, once raising sodium 3 to 5% from the starting level has mitigated the risk for cerebral edema, the balance of the correction can likely be achieved with a V2RA alone. Close monitoring of serum sodium is required no matter what regimen is selected, and the hypertonic saline can be restarted if the rise in sodium falters.

In chronic hyponatremia, V2RA likely offer an ideal treatment option for patients with euvolemic or hypervolemic hyponatremia, because they specifically reverse the pathophysiologic derangement present. Their optimal use remains to be determined, but the results of trials with all four agents are consistent and promising. The rate of rise of serum sodium induced by these agents is on the order of 6 to 9 mmol/L in the first 48 h, providing reassurance against the risk for overly rapid correction and osmotic demyelination. Furthermore, the drugs are relatively short acting. Stopping them when the rate of sodium rise is above target provides a margin of safety. No cases of osmotic myelination have been reported with V2RA. This is reassuring, but a caveat applies in that all of the studies were carried out in highly selected populations that were carefully followed by investigators with a special interest in hyponatremia. The risk will be higher when the drugs are in general use.

Tolvaptan, lixivaptan, and satavaptan are selective V2RA. Conivaptan is a combined V1a/V2 blocker. A note of caution applies when considering the use of conivaptan in patients with hypervolemic hyponatremia as a result of cirrhosis. V1aR blockade would be expected to cause splanchnic vasodilation. Whether the resulting increase in portal venous pressure or, potentially, a fall in systemic BP would increase the risk for variceal bleeding or diminish renal perfusion is unknown. More careful study is required before use of conivaptan can be routinely recommended in this subset of patients with hyponatremia.

CHF

V2RA are indicated selectively for treatment of hyponatremia caused by CHF. The carefully conducted EVEREST trials do not support the general use of tolvaptan or other V2RA for CHF per se, because no long-term survival benefit was observed. Tolvaptan or other V2RA may be of benefit in selected patients with severe congestive symptoms, because they did produce a modest benefit in the short-term EVEREST trial.

FUTURE DIRECTIONS

As stressed here, more studies to delineate the role of VRA in the treatment of acute hyponatremia are needed. Chronic hyponatremia can lead to nausea, fatigue, and cognitive impairment. Reversal of these symptoms has been the justification for treatment of chronic hyponatremia. A few studies have documented the degree of impairment with hyponatremia or improvement with correction of hyponatremia. More would be welcome. The results of V2R blockade in experimental models of polycystic kidney disease are very encouraging. Human data are awaited with great interest. Finally, the effects of V1aR blockade need more scrutiny. In particular, we need to know whether V1aR blockade is safe for patients with cirrhosis or beneficial in patients with CHF.

REFERENCES