

When Is It Appropriate to Use Vasopressin Receptor Antagonists?

Ruediger W. Leirich 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 aquaresis 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.

J Am Soc Nephrol 19: 1054–1058, 2008. doi: 10.1681/ASN.2008010089

Although patients with congestive heart failure (CHF), cirrhosis, or syndrome of inappropriate antidiuretic hormone secretion have disparate clinical features, they share common pathophysiologic mechanisms for developing hyponatremia: Failed urinary dilution associated with water retention. Lack of suppression of arginine vasopressin (AVP) release despite hypo-osmolality plays the pivotal role; therefore, patients with any of these disorders may respond to vasopressin receptor antagonists (VRA).^{1–3} The molecular target for AVP, the vasopressin 2 receptor (V2R), is one of three vasopressin receptors. The intracellular effect of ligand binding depends on the localization of the receptor (Table 1). V2R located on the basolateral membrane of collecting duct cells are G-coupled and activate the protein kinase A signal cascade, leading to fusion of preformed subapical vesicles containing membrane-bound aquaporin 2 (AQP2) into the apical membrane of collecting

duct cells. Because AQP3 and AQP4 are constitutively expressed on the basolateral membrane, insertion of AQP2 into the apical membrane is a critical limiting step in urinary concentration.

Hypovolemic hyponatremia rapidly responds to correction of volume depletion. For treating euvolemic or hypervolemic hyponatremia, however, conventional approaches have been electrolyte-free water restriction, hypertonic saline infusion, or demeclocycline, targeting an appropriately fast or slow correction, depending on the clinical situation. In practice, of course, these therapies leave much to be desired. Water restriction can be difficult to implement. It is always poorly tolerated and often of limited efficacy. Hypertonic saline may lead to volume overload or overly rapid correction of chronic hyponatremia with osmotic demyelination. Formulas used to guide dosage are complex and have been shown to predict the rate of sodium rise only variably.^{4,5} Frequent monitoring of

serum sodium during correction is always required. VRA offer a new approach to correct hyponatremia by reversing the inability to excrete free water, thus remedying the fundamental pathophysiologic lesion.

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.⁶ 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-

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Arthur Greenberg, Duke University Medical Center, Box 3014, Room 00554 Duke Hospital South, Durham, NC 27710. Phone: 919-660-6860; Fax: 919-684-4476; E-mail: arthur.greenberg@duke.edu

Copyright © 2008 by the American Society of Nephrology

Table 1. Vasopressin receptors, localization, and effects^a

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

^aAQP2, aquaporin 2; vWF, von Willebrand factor.

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

Decaux⁷ 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 hypovolemic 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.⁸

Schrier *et al.*⁹ conducted two identical trials to test the efficacy of oral tolvaptan in patients with euvolemic and hypovolemic 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 ± 4.5 mmol/L at baseline to 133.9 ± 4.8

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 ± 4.1 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 hypovolemic hyponatremia.

In smaller studies, the selective V2RA

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

Parameter	Conivaptan	Tolvaptan ^b
Characteristics		
receptor antagonism	V1a and V2	V2
route of administration	Intravenous ^c	Oral
urine osmolality	Decreased	Decreased
free water clearance	Increased	Increased
Na ⁺ excretion/24 h	Unchanged	Unchanged
Recommendations for use		
euvolemic hyponatremia (SIADH) ^d	Yes ^e	Yes, once available
hypervolemic hyponatremia (CHF) ^d	Yes ^e	Yes, once available
hypervolemic hyponatremia (cirrhosis) ^d	No, safety data lacking	Yes, once available
hypervolemic hyponatremia ^d	Never	Never
acute symptomatic hyponatremia	Not yet, insufficient data	Not yet, insufficient data
ADPKD	No data	Phase III trial ongoing
CHF	No, no data	Selected patients with severe congestive symptoms

^aADPKD, autosomal dominant polycystic kidney disease; CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

^bLike tolvaptan, lixivaptan and satavaptan are selective V2RA with similar characteristics and anticipated indications.

^cConivaptan is effective when administered orally, but only the parenteral formulation is approved by the Food and Drug Administration.

^dRefers to chronic and non-life-threatening hyponatremia.

^eFood and Drug Administration–approved indication.

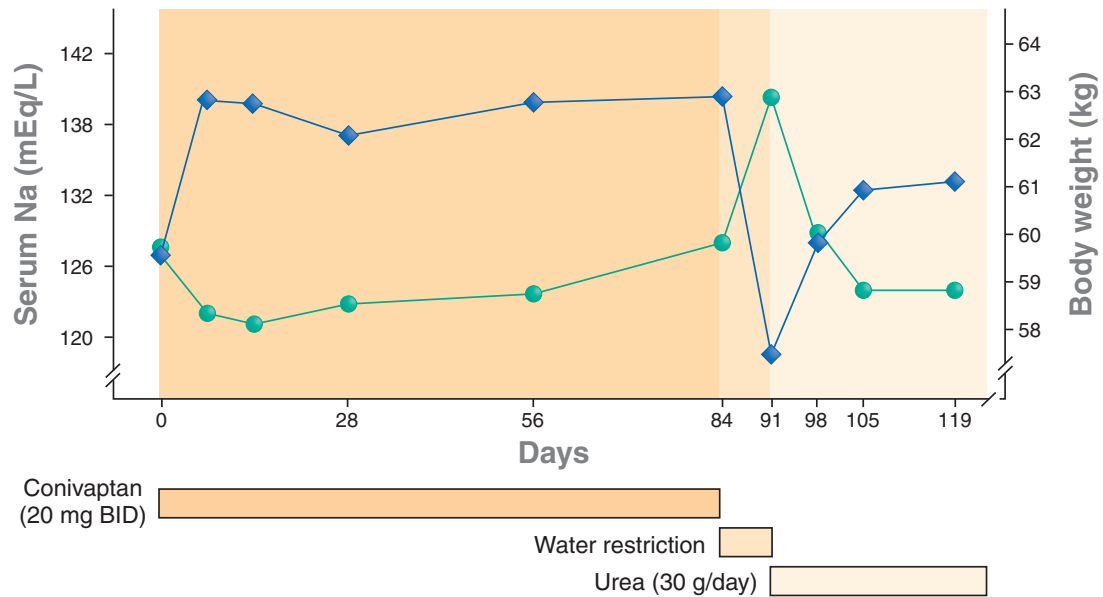


Figure 1. Patient who had chronic hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion and underwent treatment with oral conivaptan, water restriction, and urea. Changes in body weight (●) and changes in serum sodium (◆) are depicted. BID, twice a day. Reprinted from Decaux,⁷ with permission.

lixivaptan and satavaptan also were more effective than placebo in treating euvolemic or hypervolemic hyponatremia. In all of the reported trials, orthostatic hypotension, dizziness, or other symptoms of volume depletion were noted, and adjustment 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 hypothesis that outcome could be improved by interference with the maladaptive increase in AVP observed in patients with heart failure was tested in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trials.^{14,15} In two identical, short-term, multicenter, international trials, patients who were hospitalized with decompensated CHF were given either tolvaptan 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 discharge; however, the observed effect was modest and entirely driven by the difference 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 secondary 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 mortality in the long term. Importantly, the drug was well tolerated and safe. One possible conclusion to be drawn from EVEREST is that elevated AVP levels are not actually harmful in CHF; however, it is also possible that no benefit was observed because the fixed dosage of tolvaptan that was used was too low or because tolvaptan's selective 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), unopposed cAMP promotes cystogenesis by stimulating fluid secretion and cellular proliferation in evolving cysts.¹⁶ V2R act through cAMP to mediate their intracellular effect. It was hypothesized and confirmed in animal models that V2RA lower cAMP levels and retard cyst development.^{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 completed.¹⁹ A phase III trial studying the disease progression of ADPKD in patients who are receiving tolvaptan is ongoing.²⁰

WHEN AND HOW SHOULD VASOPRESSIN ANTAGONISTS BE USED?

Euvolemic and Hypervolemic Hyponatremia

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

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 osmolytes 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.²¹

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.⁹ 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 re-

quired 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.^{8–10} 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.¹⁵ 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.¹⁴

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.^{9,22} 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.²⁰ 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

- Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). *N Engl J Med* 319: 1127–1134, 1988
- Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (1). *N Engl J Med* 319: 1065–1072, 1988
- Greenberg A, Verbalis JG: Vasopressin receptor antagonists. *Kidney Int* 69: 2124–2130, 2006
- Adrogué HJ, Madias NE: Hyponatremia. *N Engl J Med* 342: 1581–1589, 2000
- Mohmand HK, Issa D, Ahmad Z, Cappuccino JD, Kouides RW, Sterns RH: Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. *Clin J Am Soc Nephrol* 2: 1110–1117, 2007
- Ohnishi A, Orita Y, Okahara R, Fujihara H, Inoue T, Yamamura Y, Yabuuchi Y, Tanaka T: Potent aquaretic agent: A novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. *J Clin Invest* 92: 2653–2659, 1993
- Decaux G: Long-term treatment of patients with inappropriate secretion of antidiuretic hormone by the vasopressin receptor antagonist conivaptan, urea, or furosemide. *Am J Med* 110: 582–584, 2001

8. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N: Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol* 27: 447–457, 2007
9. Schrier RW, Gross P, Gheorghide M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C, SALT Investigators: Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 355: 2099–2112, 2006
10. Wong F, Blei AT, Blendis LM, Thuluvath PJ: A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: A multicenter, randomized, placebo-controlled trial. *Hepatology* 37: 182–191, 2003
11. Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, Djian J, VPA Study Group: Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: A randomized double-blind multicenter trial. *Gastroenterology* 124: 933–939, 2003
12. Soupart A, Gross P, Legros JJ, Alföldi S, Annane D, Heshmati HM, Decaux G: Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V2-receptor antagonist. *Clin J Am Soc Nephrol* 1: 1154–1160, 2006
13. Klein L, O'Connor CM, Gattis WA, Zampino M, de Luca L, Vitarelli A, Fedele F, Gheorghide M: Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: Review of trials and practical considerations. *Am J Cardiol* 91: 18F–40F, 2003
14. Gheorghide M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators: Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. *JAMA* 297: 1332–1343, 2007
15. Konstam MA, Gheorghide M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators: Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA* 297: 1319–1331, 2007
16. Torres VE: Vasopressin antagonists in polycystic kidney disease. *Kidney Int* 68: 2405–2418, 2005
17. Wang X, Gattone V, Harris PC, Torres VE: Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. *J Am Soc Nephrol* 16: 846–851, 2005
18. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH: Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med* 10: 363–364, 2004
19. Chapman AB, Torres VE, Grantham JJ, Shoaf SS, Ouyang FS, Czerwiec FS: A phase IIB pilot study of the safety and efficacy of tolvaptan, a vasopressin V2 receptor antagonist (V2RA) in patients with ADPKD [Abstract]. *J Am Soc Nephrol* 16: 68A, 2005
20. Chapman AB: Autosomal dominant polycystic kidney disease: Time for a change? *J Am Soc Nephrol* 18: 1399–1407, 2007
21. Sterns RH, Cappuccio JD, Silver SM, Cohen EP: Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. *J Am Soc Nephrol* 4: 1522–1530, 1994
22. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G: Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 119: 71.e1–71.e8, 2006