New Horizons in the Pharmacologic Approach to Hyponatremia: The V₂ Receptor Antagonists

Bill F. Palmer, MD

Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.

Disclosure: B.F. Palmer received an honorarium funded by an unrestricted educational grant from Otsuka America Pharmaceuticals, Inc., for time and expertise spent in the composition of this article. No editorial assistance was provided. He also receives speaker fees from Otsuka America Pharmaceuticals, Inc.

This article provides an overview of the developing niche for vasopressin 2 receptor antagonists ("vaptans") in the management of hyponatremia in clinical practice. Specific areas of focus include the physiological and clinical rationale for use of this class of medications (including advantages over older and less specific therapeutic modalities), the practical limitations to the use of these new drugs (including issues of tolerability, toxicity, risk, and cost), and the unanswered question of the extent to which correcting hyponatremia will improve clinical outcomes. Journal of Hospital Medicine 2010;5:S27–S32. © 2010 Society of Hospital Medicine.

KEYWORDS: arginine vasopressin, AVP receptor antagonists, conivaptan, tolvaptan, hyponatremia.

Under normal circumstances, there is a balance between water intake and water excretion such that plasma osmolality and the serum sodium (Na⁺) concentration remain relatively constant. The principal mechanism responsible for prevention of hyponatremia and hyposmolality is renal water excretion. In all hyponatremic patients, water intake exceeds renal water excretion.

Excretion of water by the kidney is dependent on 3 factors. First, there must be adequate delivery of filtrate to the tip of the loop of Henle. Second, solute absorption in the ascending limb and the distal nephron must be preserved so that the tubular fluid will be diluted. Lastly, arginine vasopressin (AVP) levels must be low in the plasma. Of these 3 requirements for water excretion, the one which is most important in the genesis of hyponatremia is the failure to maximally suppress AVP levels. Given the central role of AVP in limiting renal water excretion, AVP receptor antagonists represent a physiologic and rational method to increase renal water excretion.

AVP in Regulation of Plasma Osmolality

AVP is synthesized in the supraoptic and paraventricular nucleus of the hypothalamus and then stored in the neurohypophysis (reviewed in the article “Diagnostic Approach and Management of Inpatient Hyponatremia” in this supplement). The release of AVP is exquisitely sensitive to changes in plasma osmolality. AVP is not detectable in the plasma at an osmolality below approximately 280 mOsm/kg but increases in a nearly linear fashion beginning with as little as a 2% to 3% increase in osmolality above this value. The extreme sensitivity of this system allows for plasma osmolality to be maintained within a narrow range.

A second major determinant of AVP release is the effective arterial blood volume. While AVP levels are very sensitive to plasma osmolality, small changes of <10% in blood pressure or blood volume have no effect on AVP levels. However, once decreases in volume or pressure exceed this value, baroreceptor-mediated signals provide persistent stimuli for AVP secretion. Baroreceptor-mediated AVP release will continue even when plasma osmolality falls below 280 mOsm/kg. Teleologically, this system can be viewed as an emergency mechanism to defend blood pressure. Thus, small decreases in blood volume and blood pressure will cause the body to retain NaCl which will raise osmolality and lead to water retention. However, if NaCl is not available and if blood pressure and volume are becoming dangerously low (down 10%), the body behaves as if defense of blood pressure is more important than defense of osmolality, and AVP is secreted. The specific compartment whose volume is sensed in order to determine AVP secretion in this setting is the effective arterial volume. This overriding effect of volume explains the persistence of high AVP levels in hyponatremic patients with conditions such as heart failure and cirrhosis.

Other stimuli for the release of AVP include pain, nausea, and hypoxia. Inappropriate release of AVP can occur with a variety of central nervous system and pulmonary diseases as well as with drugs, particularly those that act within the central nervous system. Certain tumors can synthesize and release AVP.

AVP exerts its effects on cells through 3 receptors (Table 1). The V₁A receptor is expressed in a variety of tissues but is primarily found on vascular smooth muscle cells. Stimulation of this receptor results in vasoconstriction, platelet aggregation, inotropic stimulation and myocardial protein synthesis. The V₁B receptor is expressed in cells of the anterior pituitary and throughout the brain. Stimulation of this receptor results in release of adrenocorticotropic hormone (ACTH). Stimulation of the V₁A and V₁B receptors activate phospholipase C leading to increases in inositol
trisphosphate and diacylglycerol with secondary increases in cell calcium and activation of protein kinase C.

The V₂ receptor is found on the basolateral surface of the renal collecting duct and vascular endothelium where it mediates the antidiuretic effects of AVP and stimulates the release of von Willebrand factor respectively. Unlike the V₁A and V₁B receptors, binding of AVP to the V₂ receptor activates the Gₛ-coupled adenyl cyclase system causing increased intracellular levels of cyclic adenosine monophosphate (cAMP). In the kidney, generation of cAMP stimulates protein kinase A which then phosphorylates preformed aquaporin-2 water channels causing trafficking and insertion of the channels into the luminal membrane of the tubular cells.³ The insertion of the aquaporin-2 protein renders the collecting duct selectively permeable to water, which is then reabsorbed from the tubular lumen into the blood driven by the osmotic driving force of the hypertonic interstitium. In the absence of AVP, aquaporin membrane insertion and apical membrane water permeability are dramatically reduced.

Physiologic Rationale for Use of AVP Antagonists

AVP antagonists block the V₂ receptor located on the basolateral surface of the collecting duct thereby antagonizing the ability of AVP to cause insertion of the aquaporin-2 water channels into the luminal membrane. The increase in urine output is similar in quantity to diuretics but differs in content. V₂ receptor antagonists increase water excretion with little to no change in urinary electrolytes. As a result, lowering of the serum K⁺ level, metabolic alkalosis, and increases in the serum creatinine and blood urea nitrogen concentration are avoided in contrast to diuretics such as furosemide and hydrochlorothiazide. In addition, orthostatic hypotension and activation of neurohumoral effectors such as angiotensin II, circulating catecholamines, and aldosterone are not features of V₂ receptor blockade. These differences have lead to V₂ receptor antagonists being characterized as “aquaretic” agents so as to distinguish them from diuretics.

The physiologic rationale for use of V₂ receptor antagonists is best exemplified by considering the relationship between the serum Na⁺ concentration and the total body content of Na⁺, K⁺, and water approximated by the equation:

\[
\text{Plasma Na}^+\text{ concentration} \approx \frac{\text{Total body Na}^+ + \text{Total body K}^+}{\text{Total body water}}
\]

According to this equation, increasing the plasma Na⁺ concentration can be achieved through the administration of salt. This approach is clearly the treatment of choice in patients who are total body salt depleted. By contrast, in euvoletic and particularly in hypervolemic patients, such a strategy can cause potential worsening of the underlying disorder as in edematous patients with congestive heart failure or cirrhosis. In these patients selectively reducing the denominator is the preferable strategy to raise the plasma Na⁺ concentration. The aquaretic properties of the V₂ receptor antagonists are well suited for this purpose.

The first specific V₂ receptor antagonists synthesized were peptide analogues of AVP. This approach was later abandoned due to agonist effects noted upon chronic administration. Development of nonpeptide antagonists capable of interacting with the receptor so as to prevent binding of native AVP without themselves stimulating the receptor are now in various stages of clinical development.³ Tolvaptan, satavaptan, and lixivaptan are selective for the V₂ receptor and are administered orally (Table 2). Conivaptan is an intravenous agent with blocking effects on both the V₂ and V₁A receptor. These drugs (the vaptans) have been shown to be effective in increasing the serum Na⁺ concentration in patients with modest asymptomatic hyponatremia. They can be considered in patients with euvoletic and hypervolemic (diutional) hyponatremia but should not be used in patients with hypovolemic hyponatremia.

**Clinical Use of AVP Antagonists**

Conivaptan (an intravenous V₁A-V₂ receptor antagonist) is approved by the Food and Drug Administration (FDA) for euvoletic and hypervolemic hyponatremia. The
effective the drug was demonstrated in a randomized placebo controlled trial of 84 hospitalized patients with euovolemic or hypervolemic hyponatremia in which the serum Na\(^+\) ranged from 115 to <130 mEq/L.\(^5\) The patients were given a 20-mg loading dose followed by a continuous infusion of either 40 or 80 mg daily for 4 days. Conivaptan significantly raised the serum Na\(^+\) concentration by 6.3 and 9.4 in the 40 and 80 mg/day arms respectively as compared to 0.8 mEq/L in the placebo group.

Conivaptan is also active as an oral formulation but its distribution has been restricted to parenteral use for short-term (4 days maximum) in-hospital administration only. This restriction is due to potent inhibitory effects of the drug on the hepatic cytochrome P\(_{450}\) 3A4 enzyme system and the potential for untoward drug interactions. The inhibitory effects of other members of this class on the cytochrome P450 3A4 (CYP3A4) system are more limited, allowing for oral formulations to be used in a clinical setting.

Tolvaptan is the only other AVP antagonist currently approved by the FDA. Unlike conivaptan, tolvaptan is an oral agent with effects confined to the V\(_2\) receptor. The drug is indicated for the treatment of clinically significant hypervolemic and euovolemic hyponatremia.

The efficacy of tolvaptan was evaluated in 2 simultaneously conducted multicenter, randomized, double blind trials called Study of Ascending Levels of Tolvaptan in hyponatremia 1 and 2 (SALT 1 and SALT 2).\(^5\) The 2 studies together randomized 225 patients with euovolemic or hypervolemic hyponatremia to outpatient treatment with the study drug for 30 days and 223 patients to placebo. Patients with a serum Na\(^+\) of <120 mEq/L in association with neurologic impairment were excluded from the trial. Serum Na\(^+\) increased more in the tolvaptan group than in the placebo during the first 4 days (3.62 vs. 0.25 mEq/L). After 30 days of therapy serum Na\(^+\) concentrations were 6.22 higher in the tolvaptan group compared with 1.66 mEq/L in the placebo group. When tolvaptan was discontinued at study end, the serum Na\(^+\) fell over a seven day period to a value similar to that in the placebo treated patients. Four patients (1.8%) exceeded the study goal of limiting correction of the hyponatremia to <12 mEq/L in the first 24 hours of treatment, but none of these patients developed adverse clinical sequelae.

As previously mentioned conivaptan and tolvaptan are indicated for the treatment of hyponatremia in the setting of euvolesia or hypervolemia. These drugs should not be used in hypovolemic states since the increase in renal water excretion can potentially predispose to worsening hemodynamics in the setting of volume depletion. To be sure, any volume of water removed from the body is principally derived from the intracellular compartment (two-thirds) and would not be expected to affect blood pressure to a major extent. However, one-twelfth of any water volume loss is derived from the circulating compartment and could potentially aggravate a borderline low blood pressure in the setting of volume depletion.

This concern is particularly true for conivaptan and its blocking effects on the V\(_1a\) receptor. AVP can cause peripheral vasoconstriction by stimulating the V\(_1a\) receptor on the peripheral vasculature.\(^7\) However, circulating concentrations observed in euovolemic and hypervolemic conditions are not typically of a magnitude to elicit this effect thus explaining the lack of clinically significant hypotension in clinical trials. By contrast, AVP may reach a high enough concentration and play a contributory role in the maintenance of blood pressure under conditions of significant depletion of extracellular fluid volume (hemorrhage) or in states of generalized vasodilation such as sepsis or advanced cirrhosis. In these settings blockade of the V\(_1a\) receptor may result in significant hypotension.

Another theoretical concern of blocking the V\(_1a\) receptor with conivaptan is the potential to cause further sequestration of fluid in the splanchnic vascular bed and theoretically increase the risk of hepatorenal syndrome.\(^8\) The importance of splanchnic vasodilation in the genesis of renal hypoperfusion has been indirectly illustrated by the response to ornipressin, an analog of AVP that is a preferential splanchnic vasoconstrictor. The administration of ornipressin to patients with advanced cirrhosis leads to correction of many of the systemic and renal hemodynamic abnormalities that are present. These include an elevation in mean arterial pressure, reductions in plasma renin activity and norepinephrine concentration, and increases in renal blood flow, glomerular filtration rate, and urinary sodium excretion and volume. V\(_1a\) receptor blockade has the potential to increase the degree of arterial vasodilation in the splanchnic arteriolar bed. Increasing degrees of splanchnic vasodilation contribute to a fall in mean arterial pressure and unloading of baroreceptors in the central circulation. As a result, central afferent sensors signal the activation of neurohumoral effectors which in turn decrease perfusion of other organs, particularly the kidney.

**AVP Antagonists in Severe Symptomatic Hyponatremia**

Symptoms of hyponatremia include nausea and malaise, which can be followed by headache, laryngus, muscle cramps, restlessness, confusion and disorientation.\(^9\) Life threatening symptoms are those of impending brain herniation and include seizures, decreased levels consciousness, and obtundation. Hypertonic saline remains the treatment of choice in those patients who are clinically determined to be severely symptomatic.\(^10\) Vaptan therapy does result in a brisk and relatively prolonged water diuresis. Indeed, in the first 6 hours following the parenteral administration of conivaptan there is a several mEq/L increase in the serum Na\(^+\) concentration.\(^5\) Whether this time course of correction is sufficient to abort fatal hyponatremic encephalopathy is simply not known. Such patients to date have been excluded from clinical studies since randomization in a placebo-controlled trial would be clearly unethical in such subjects, and not using hypertonic saline might also be considered unsafe

2010 Society of Hospital Medicine DOI 10.1002/jhm.785
Published online in Wiley InterScience (www.interscience.wiley.com).
Although not well studied, one could coadminister conivaptan along with hypertonic saline and anticipate a more rapid initial rise in the serum Na\(^+\). Once stabilized, the hypertonic saline could be discontinued and the remainder of correction be accomplished by use of the receptor antagonist alone. This strategy would help to minimize the likelihood of volume overload due to the use of hypertonic saline but would require frequent monitoring of the serum Na\(^+\) to ensure the rate of correction was within accepted guidelines.

AVP Antagonists in Patients With Mild to Moderate Symptoms of Hyponatremia

Hospitalized patients with mild to moderate symptoms of hyponatremia can be considered ideal candidates for the use of V\(_2\) receptor antagonists. Both conivaptan and tolvaptan can be expected to increase the serum Na\(^+\) concentration to a greater extent and more predictably than fluid restriction alone. The superiority of these drugs would be particularly evident in those who require ongoing fluid administration for any number of reasons such as parenteral administration of antibiotics or proton pump inhibitors.\(^{11}\)

In hyponatremic patients with decompensated heart failure there may be changes in mental status in which it is difficult to separate out the contribution of hyponatremia from the decrease in cerebral perfusion. Vaptan therapy offers a predictable way to improve the serum Na\(^+\) contribution over an acceptable period of time thereby removing one of the variables. Even if hyponatremia is not the direct cause of symptoms, it may lower the threshold for mental status changes resulting from poor cerebral perfusion. A similar argument for vaptan therapy can be made in hyponatremic patients with cirrhosis. In this population mental status changes can be due to the hyponatremia, the underlying liver disease, or both. If no improvement occurred following the correction of the hyponatremia, therapy could then be focused on the underlying liver disease. In fact, in any delirious patient with hyponatremia, correction of the underlying electrolyte disorder can help to clarify the degree to which the hyponatremia is exacerbating the altered mental status.

There are no head to head studies comparing conivaptan and tolvaptan in patients with mild to moderate symptoms of hyponatremia. Presumably both drugs would work with similar efficacy. Conivaptan therapy can be complicated by phlebitis when administered through a peripheral vein due to the irritative effects of polypropylene glycol which serves as a diluent for the drug.\(^{12}\) For this reason the drug is often given through a central vein. The theoretical risk of conivaptan's V\(_{1a}\) receptor blocking effects in patients with cirrhosis has already been discussed. Tolvaptan is given orally starting at 15 mg daily. Depending on the response the dose can be increased to 30 mg and ultimately to 60 mg daily. Few patients in the SALT 1 and 2 trials required the 60 mg dose.

Measurement of the urine osmolality may be useful in predicting how responsive a patient will be to the administration of a vaptan. In this regard, urine osmolality can be thought as a biomarker of the effect of AVP on the renal collecting duct.\(^{13}\) The higher the urine osmolality, presumably the higher the serum AVP level or the greater the effect of AVP is on the tubule. By contrast, those with a lower urine osmolality presumably have less AVP effect on the tubule and therefore will manifest a less robust response to a V\(_2\) receptor blocker.

There are circumstances unique to the hospitalized patient where one may consider use of a V\(_2\) receptor antagonist. Consider a patient admitted with pneumonia complicated by hyponatremia (Na\(^+\) = 128 mEq/L) due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH) who is treated with intravenous antibiotics, stabilized, and is now being considered for discharge. Despite fluid restriction the serum Na\(^+\) concentration is currently 126 mEq/L and the admitting physician is reluctant to discharge the patient for fear the Na\(^+\) may fall further and result in symptomatic hyponatremia. The hospital discharge is postponed and fluid restriction is intensified. Two days later the serum Na\(^+\) concentration has risen to 131 mEq/L and the patient is discharged. While one can question the wisdom of postponing the original planned discharge based on the lab value alone, this type of scenario is common in clinical practice. Fluid restriction is poorly tolerated, difficult to enforce, and often unpredictable in response. The administration of a single dose of a V\(_2\) receptor antagonist is a reliable way to increase the serum Na\(^+\) concentration over a 24 hour period and in this case could have potentially shortened the hospital stay.

Consider another patient admitted with a hip fracture who is found to have a serum Na\(^+\) concentration of 126 meq/L attributed to ongoing use of an antidepressant agent. The patient is otherwise medically stable but the anesthesiologist is unwilling to accept the patient for surgery until the serum Na\(^+\) is at least >130 mEq/L. Fluid restriction is prescribed and only 2 to 3 days later has the serum Na\(^+\) reached a value of 131 mEq/L. Once again, administration of a vaptan would have almost certainly increased the Na\(^+\) concentration to the desired threshold over a 24 hour period, allowing the patient to undergo the surgical procedure without experiencing the undue delay.

In each of these scenarios short term use of a vaptan would provide for a more rapid and predictable increase in the serum Na\(^+\) concentration and potentially decrease the length of hospital stay in comparison to fluid restriction alone. In addition to being less predictable and often poorly tolerated, fluid restriction is often ineffective due to the obligatory fluid administration hospitalized patients require for other therapies or nutrition. Demeclocycline and lithium have been used to antagonize the effects of AVP on the tubule but these drugs take several days before any demonstrable increase in renal water excretion is seen. Demeclocycline antagonizes the effect of AVP through nephrotoxic effects on the tubular cell whereas vaptan's are competitive inhibitors of the V\(_2\) receptor and are not associated with nephrotoxicity. Lithium interferes in the intracellular...

2010 Society of Hospital Medicine DOI 10.1002/jhm.785 Published online in Wiley InterScience (www.interscience.wiley.com).
signaling pathways by which AVP causes insertion of water channels into the apical membrane. The doses required to illicit an increase in renal water excretion are near those which can result in lithium levels sufficient to cause neurotoxicity. The primary side effect of vaptan therapy are those one would predict from inducing an aquaretic effect and include thirst, increased urinary frequency, and increased urinary volume.

The decision to use a vaptan on a more prolonged basis is made on a case by case basis. When the underlying cause of increased AVP is deemed to be chronic and irreversible then therapy can be extended to the outpatient setting. Consideration for more chronic therapy would be appropriate for patients with SIADH due to underlying cancer, or those with severe chronic congestive heart failure or advanced cirrhosis. If the cause of the increased AVP is transient, then 1 to 2 doses of a vaptan while in the hospital may be all that is required. Transient causes of increased AVP would include drug related causes, acute pneumonia, hypoxia associated with respiratory failure, and acute decompensated heart failure. Once again vaptan therapy should not be used when the cause of increased AVP is due to total body salt depletion.

AVP Antagonists in Asymptomatic Hyponatremic Patients
One remaining question concerning the use of vaptan therapy is whether they are helpful in hyponatremic patients who are asymptomatic. There are several observations which raise the possibility that patients deemed to be otherwise asymptomatic do in fact have subtle abnormalities attributable to the low Na⁺ concentration and therefore could benefit if the hyponatremia was corrected. First, some patients with a serum Na⁺ in the range of 120 mEq/L to 129 mEq/L have subtle neurolologic changes that improve following correction of the serum Na⁺ concentration. In this regard, case control studies have shown an association between hyponatremia and risk of falls and fractures particularly in the elderly population. Chronic hyponatremia has been shown to cause a reduction in bone mass in an experimental model of SIADH and hyponatremia is associated with osteoporosis in cross-sectional human data. Fall-related injury is associated with substantial adverse psychological and physical outcomes and is a cause of both death and disability in this population. It would be of considerable socioeconomic benefit if treatment of asymptomatic hyponatremia were able to reduce the risk of this complication.

Lastly, hyponatremia is associated with increased morbidity and mortality but generally the low Na⁺ concentration is merely thought to be marker of the severity of the underlying disease and not a direct contributor to the adverse outcome. For example in decompensated heart failure there is an inverse relationship between the degree of hyponatremia and the extent of neurohormonal activation. Adverse effects resulting from persistent activation of the renin-angiotensin-aldosterone system and sympathetic nerve activity are thought to be the mechanism underlying the increase in mortality in hyponatremic patients with heart failure. Nevertheless, it has been suggested that hyponatremia itself, the associated hypotonicity, and/or elevated levels of AVP might exert adverse effects on the cardiovascular system or other organ systems and therefore play a contributory role in patient morbidity and mortality. While it remains speculative as to whether correction of the hyponatremia per se will improve patient outcomes, the V₂ receptor antagonists offer an opportunity to test this uncertainty in patients with euvolemic and hypervolemic hyponatremia.

Address for correspondence and reprint requests:
Biff F. Palmer, MD, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390; Telephone: 214-648-7848; Fax: 214-648-2071; E-mail: biff.palmer@utsouthwestern.edu Received 24 February 2010; revision received 19 March 2010; accepted 29 March 2010.

References