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Treatment of the Syndrome of Inappropriate Antidiuretic Hormone Secretion and the Emergence of Vasopressin Antagonists for Hyponatremic Disorders

By TOMAS BERL, MD

Since the original description of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), its treatment has posed a challenge to physicians. The recognition that hyponatremia, the hallmark of the disorder, is primarily a consequence of water retention mediated by the secretion of antidiuretic hormone (ADH), led to attempts to inhibit the secretion of this hormone. Several approaches have been developed to correct this syndrome; however, until recently, none has proven to be an ideal treatment strategy. This issue of *Nephrology Rounds* reviews the development of the vasopressin antagonists (vaptans) and their advent into clinical practice and the possibility of a new era in the treatment of hyponatremic disorders.

The past and the present

Ethanol was the first recognized inhibitor of ADH secretion and was employed in experimental settings to develop a vasopressin bioassay. The extension of this property of ethanol to humans with SIADH was obviously unacceptable. Thereafter, a number of therapeutic approaches were employed to correct hyponatremia, both in the acute and chronic setting. Specifically, in the former, both hypertonic saline and normal saline were utilized. There is general agreement that hypertonic saline should be employed in acutely hyponatremic subjects displaying central nervous system (CNS) symptoms in order to rapidly increase serum tonicity and decrease cerebral edema that occurs, for example, with exercise-associated hyponatremia.¹ The administration of saline, however, is of limited therapeutic benefit in patients with the SIADH secretion. Since these patients characteristically have urinary sodium (Na) plus urinary potassium (K) concentrations that exceed the plasma Na concentration, the administration of saline results in further worsening of hyponatremia. This has been illustrated in the postoperative period, characterized by elevated vasopressin levels. In such patients, the administration of primarily isotonic fluids can result in a decrease in the serum Na concentration, the so-called "desalination phenomenon."² In order to generate urine that provides electrolyte-free water excretion, an alternative was suggested involving the use of a loop diuretic.³ In this approach, the administration of the diuretic is followed by measurement of the excreted Na that is then replaced in a small volume of hypertonic saline or a larger volume of isotonic saline, yielding a net negative water balance, while maintaining a neutral Na balance.⁴ This treatment is effective, but requires intensive patient monitoring and is subject to calculation errors. As a result, this approach has not achieved widespread acceptance and use.

Agents that antagonize the hydro-osmotic effect of vasopressin action at the level of the collecting duct would appear to be the ideal drugs to treat the syndrome. Pharmacologic agents such as lithium⁵ and demeclocycline⁶ were discovered in the 1970s to cause nephrogenic diabetes insipidus and were adapted for use in SIADH. However, the well-known neurological and renal toxicities of lithium⁷ quickly limited its use. Therefore, demeclocycline rapidly emerged as the safer and more effective of the two drugs.⁸ Unfortunately, this antibiotic also carries significant toxicity, including a variety of gastrointestinal symptoms, photosensitivity, as well as nephrotoxicity in patients with liver



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disease. Because it is so poorly tolerated, demeclocycline is far from an ideal treatment modality.

With the paucity of good pharmacologic options, water restriction has been the cornerstone of treatment for hyponatremia in the SIADH, as well as in other pathologic states associated with high ADH levels. Since the development of hyponatremia clearly requires the intake of water, this approach addresses the pathophysiology of the disorder and represents the most economical option. However, water restriction also carries significant limitations, not the least of which is difficulty with compliance. Water intake is habitually driven and patients with the syndrome may, in fact, have a primary increase in thirst perception. Furthermore, according to an analysis by Furst et al,⁹ the degree of water restriction that is frequently prescribed (1 liter) is rarely appropriate and usually insufficient. In fact, essentially no degree of water restriction will ameliorate the condition when the diluting defect is severe (ie, reflected by a urine/plasma electrolyte ratio that is >1). Finally, attempts to increase urine flow by supplements of urea are effective, but also associated with undesirable gastrointestinal side effects that make it most unpalatable. As a result, the development of therapeutic agents that would improve on the present-day armamentarium of options would be most welcome. Such is the case of the emerging vasopressin antagonists.

The future: vasopressin antagonists

Given the relatively simple structure of the parent hormone, biochemists have developed vasopressin analogs for over 3 decades. Among others, this resulted in the development of desmopressin, a long-acting agonist of the vasopressin-2 (V2) receptor. Subsequently, a number of potential peptide antagonists were synthesized in an attempt to antagonize the hormone's action.¹⁰ Unfortunately, even if devoid of agonistic effects, they proved to have considerable species variability and, some that were effective in experimental animals, were not effective in human trials.¹¹ Furthermore, the oral bioavailability of peptides is limited, requiring parenteral administration.

The development of orally-active nonpeptide vasopressin antagonists promptly followed and, in 1993, the first such compound was shown to produce a water diuresis (aquaresis) in normal subjects.¹² This was soon followed by the development of other highly potent and selective inhibitors of the V2 receptor.¹³ Antagonists presently under clinical development are listed in Table 1. Structurally, they are all benzazepine or oxindole derivatives and, with the exception of conivaptan, which is both a V1_a and V2 receptor antagonist, the others are selective for the V2 receptor. These agents displace radioactively-labeled hormone from its receptor and thereby potently inhibit arginine vasopressin (AVP) stimulation of adenylate cyclase.^{13,14} More recently, molecular

Table 1: Adverse events in the SALT I and SALT II Trials

Non-peptide AVP receptor antagonists				
	Tol-vaptan	Lixi-vaptan	Sata-vaptan	Coni-vaptan
Receptor	V2	V2	V2	V1 _a /V2
Route of administration	Oral	Oral	Oral	IV
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Na ⁺ excretion 24 hours	↔	↔ low dose ↑ high dose	↔	↔
Company	Otsuka	CardioKine	sanofi-aventis	Astellas

Modified from Lee et al, *Am Heart J* 146:9, 2003

modeling has revealed that the binding sites for arginine vasopressin and the antagonists only partially overlap; whereas, the native hormone binds to the extracellular surface of the receptor and the antagonists penetrate into the transmembrane region, as illustrated in Figure 1.¹⁵

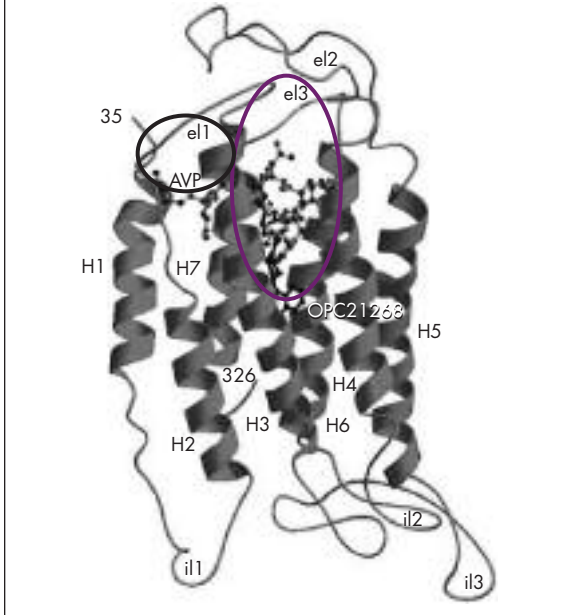
Vasopressin antagonists in the SIADH

Following the successful use of the first-generation oral vasopressin antagonist – OPC31260 – in an experimental model of SIADH in rats,¹⁶ 11 patients with the syndrome were treated with the drug.¹⁷ The authors described a transient decrease in urinary osmolality and an increase in urine volume that was independent of changes in solute excretion. The agents listed in Table 1 have also been used in patients with SIADH. Specifically, 6 patients given 50 to 100 mg bid of lixivaptan achieved a serum Na of 133 mmol/L, compared with 126 mmol/L for those on placebo. This increment in serum Na was associated with a decrease in urinary Na excretion, presumably as a consequence of the volume expansion correction that accompanied the aquaretic response.¹⁸ As part of the North American Lixivaptan study, 4 patients with SIADH who received the drug increased their serum Na concentration from 127 to 139 mmol/L over a 7-day period.¹⁹

The largest studies employing a vasopressin antagonist (tolvaptan) are the SALT I and SALT II trials, in which 91 of the 214 patients who received the active drug had SIADH.²⁰ The effect of tolvaptan and placebo on serum Na over the 30 days of the study and 7 days after discontinuation is shown in Figure 2. At all time-points, serum Na was higher in tolvaptan-treated subjects and the effect was reversible as the serum Na decreased to levels seen in subjects on placebo after 7 days. In this study, after 30 days of treatment, the mean increase in serum Na in the SIADH patients was 8.2 mmol/L, an increase that was greater than that seen in patients with congestive heart failure or cirrhosis in the same study.

Figure 1: AVP vs AVP antagonist binding¹⁵

The vasopressin receptor with its 7 transmembrane regions (H1-H7), extracellular (e) and intracellular domains (il). The site at which AVP binds at the surface of the receptor, circled in maroon. The site of the antagonist binding is deep in the transmembrane region and is circled in black. The sites are distinct and partially overlap. The antagonist prevents the binding of AVP.

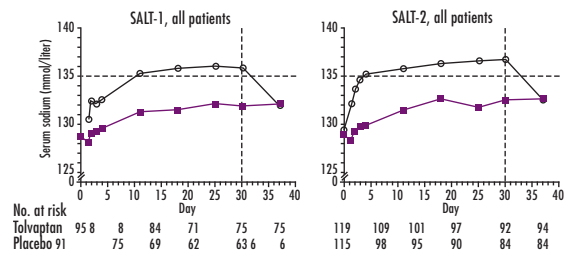


The increment in serum Na was accompanied by an improvement in the mental component of the Medical Outcome Health Survey Short Form-12 (SF-12) survey.²⁰

Likewise, in 26 patients with SIADH, satavaptan increased serum Na from 125 to 136 mmol/L over 5 days on 25 mg and to 140 mmol/L with 50 mg of the drug. A longer-term open-label extension revealed persistent efficacy without escape from the drug's effects. Finally, conivaptan was effective in raising serum Na over several months in 2 patients with chronic SIADH who did not respond to water restriction.²² A recent report with this agent also confirms its efficacy over a 5-day period in a study that included 38 euvoletic patients, most of whom most likely had SIADH.²³ However, because conivaptan interacts with other drugs that are metabolized by the CYP3A4 pathway, the oral preparation is not being further developed and the antagonist will be available only in the intravenous (IV) form. In fact, in this form, conivaptan is the first, and so far, the only vasopressin antagonist approved by the United States Food and Drug Administration (FDA) for use in euvoletic hyponatremia.²⁴ This approval was based on double-blind, randomized clinical studies of 56 patients with euvoletic hyponatremia, of whom 35 received a 20 mg bolus of conivaptan followed by continuous infusion of either 40 (n=18) or 80 (n=17) mg/day for 4 days on a background of a 2 L water restriction. At the end of 4 days, the patients on the 40 mg/day infusion had an increase in their serum

Figure 2: Effect of tolvaptan (15-60 mg) on serum sodium concentration in two trials²⁰

The serum Na was significantly higher in tolvaptan-treated patients (open circles) than on placebo (maroon squares).



Na by 6.1 mmol/L. At the end of the same time period (4 days), 82% of the patients receiving 80 mg/day increased their serum Na by >6 mmol/L,²⁵ which was significantly greater than that seen in the placebo group ($p < 0.05$). The increase in serum Na occurred more rapidly than with oral administration, since the median time to an increase in serum Na by 4 mmol/L was approximately 23 hours with both IV doses.²⁵ At this time, the use of IV conivaptan is restricted to hospitalized patients with chronic euvoletic hyponatremia. Specifically, it is not used as an alternative to 3% sodium chloride (NaCl) in symptomatic hyponatremic patients.

Vasopressin antagonists in hypervolemic states

Persistent vasopressin release mediated by nonosmotic pathways underlies the mechanism of hyponatremia frequently seen in congestive heart failure and cirrhosis.^{26,27} It is not surprising that the vasopressin antagonists have been studied in patients with these disorders.

Cirrhosis

A considerable number of patients with cirrhosis have been exposed to vasopressin antagonists. Decaux described the effect of lixivaptan in 5 such patients whose mean serum Na rose from 128 to 133 mmol/L over a 72-hour period on 50 to 100 mg bid of the drug.¹⁸ In contrast to the decrease in Na excretion that accompanies correction in the SIADH, these patients sustained a mild natriuresis. Guyader et al performed a pharmacodynamic study with ascending single doses of the drug from 25 to 300 mg, and observed a dose-dependent aquaretic response and a small natriuretic response in 27 patients with cirrhosis.²⁸ A similar dose-dependent effect was observed in the North American trial, as 33 patients with cirrhosis received either placebo, 25, 125, or 250 mg bid of lixivaptan.¹⁹ While the serum Na was unchanged at 7 days in the placebo group, it rose by 3, 5, and 7 mmol/L in the other 3 groups, respectively. Finally, in a larger, multicenter, European trial involving 60 patients on either placebo, 50, or 100 mg bid of lixivaptan, at 7 days, those on placebo had no change in serum Na, while those

on 100 mg bid had an increase of 6 mmol/L. In fact, 50% of the patients in this group normalized their serum Na, as defined by a level of >136 mmol/L.²⁹

The precursor to tolvaptan, OPC31260, was described as causing a water diuresis in subjects with cirrhosis³⁰ and, in the aforementioned SALT II trial, approximately 30% of the 223 patients studied had cirrhosis. When compared with those on placebo, the patients with cirrhosis had a greater increase in serum Na at 30 days (1.5 versus 4.0 mmol/L), a more modest increase than that seen in the SIADH group. In fact, 37% of the cirrhotic patients appeared to be resistant to the drug. Because conivaptan has V_{1a} receptor blocker activity, it has not been used in patients with cirrhosis. Concerns that the drug could cause hypotension and variceal bleeding make only the V₂ receptor antagonists appropriate for this population. Furthermore, the data obtained with lixivaptan and tolvaptan are not in full accordance and only further clinical experience will ascertain the role of these agents in the management of hyponatremia in patients with cirrhosis.

Congestive heart failure (CHF)

In view of the well-established role for neurohumoral pathways in the pathogenesis of CHF, the possibility of adding vasopressin blockade to the sympathetic and renin-angiotensin-aldosterone system appears attractive.³¹ Therefore, it is not surprising that the vasopressin antagonists have been extensively investigated in these patients, particularly tolvaptan.

In a double-blind randomized trial, Gheorghiadu et al studied 254 patients with class II or III CHF, 28% of whom were hyponatremic (serum Na <136 mmol/L).³² The patients were given placebo, 30, 45, or 60 mg of tolvaptan daily for 25 days, while being maintained on furosemide, but not water-restricted. The patients on all doses of the vasopressin antagonist lost weight (approximately 1 kg) and maintained it for the duration of the study. The serum Na rose by 3 mmol/L in the first 24 hours, but then drifted back to baseline over the ensuing days of the study. However, among the patients who were hyponatremic at baseline, 80% of those on tolvaptan versus 40% of those on placebo normalized their serum Na within 1 day and maintained it throughout the duration of the study.

In a subsequent study, the same group examined the effects of 30, 60, or 90 mg of tolvaptan in 319 hospitalized patients with CHF and ejection fractions <40%.³³ Patients on active drug had greater in-hospital weight loss than those on placebo. In the hyponatremic patients, the changes in serum

Na were similar to those of the previous study. A post hoc analysis revealed a trend towards a decrease in mortality in the subgroup with renal insufficiency and more severe CHF. However, this trial was not powered to assess the impact on overall cardiovascular survival.

The large, multicenter trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan [EVEREST]), randomized 4133 patients hospitalized for heart failure to either 30 mg/d of tolvaptan or placebo. The study found no difference between the groups as to the primary outcomes of the trial – all-cause mortality, cardiovascular mortality, or heart failure hospitalizations – but there was a favorable effect on patient-assessed dyspnea.³⁴ It must be noted that only 8% of the patients had a serum Na <134 mmol/L. This group sustained an increase in serum Na of 5.49 mmol/L compared to 1.85 mmol/L in the placebo group ($p<0.001$). While the study reported no differences in outcomes in patients with serum Na above and below 137 mmol/L, it is not clear whether the more severely hyponatremic group would have benefited since their numbers were too low for a meaningful independent analysis. The increment in serum Na seen in this trial is comparable to that observed in 24 patients in the SALT II trial. Specifically, these patients had an increase in their serum Na of 6 mmol/L at 30 days (intermediate between the response of the SIADH and cirrhosis patients). Finally, lixivaptan was given to 30 heart failure patients who required diuretics. At doses of 30 to 400 mg, the drug increased urine volume and, in high doses, serum Na increased as well.³⁵

In view of its combined V_{1a}/V₂ receptor antagonism, conivaptan would appear to be particularly desirable in patients with CHF. An acute hemodynamic study has been reported in which 142 patients with CHF and NYHA class III and IV were given placebo or a single IV dose of 10, 20, or 40 mg of conivaptan.³⁶ The drug decreased capillary wedge and right atrial pressure to a greater degree than placebo, in association with an increase in urine flow and a decrease in urinary osmolality. Other hemodynamic parameters, including mean arterial pressure, cardiac index, and systemic vascular resistance were unchanged. Whether the effect on capillary wedge pressure is due to a V_{1a} receptor-mediated vasodilatation or V₂-mediated aquaresis could not be established. It should be noted that conivaptan has also been approved for use in patients with CHF.

Safety considerations

As is the case with the development of any class of new drugs, potential safety considerations and

Table 2: Adverse events in the SALT I and SALT II Trials

Events that occurred 2x more frequently with tolvaptan than with placebo		
	Tolvaptan n=223	Placebo n=220
Dry mouth	13 %	4 %
Thirst	14 %	5 %
Urinary frequency	7 %	3 %
Constipation	7 %	2 %
Hyperglycemia	5 %	1 %

Modified from Schrier RW, et al, *N Engl J Med* 2006;355:2099

monitoring of adverse effects is of primary importance. In regards to vasopressin antagonists, one of the concerns is the possibility of increasing serum sodium too rapidly thereby putting patients at risk for osmotic demyelination. To the knowledge of these authors and others with extensive experience.²⁴ To the knowledge of these authors and others with extensive experience, no such case has been reported as yet. It must be noted, however, that in the setting of clinical studies, changes in serum Na were carefully monitored and there were measures in place to prevent undue increases. Also, the studies were carried out with minimal, if any, water restrictions. Adverse effects occurred at least twice as frequently in the tolvaptan group compared with placebo in both SALT trials and are listed in Table 2. Interestingly, one of the frequent complaints reported by patients on these agents is dry mouth and thirst. These effects were also observed in the EVEREST trial.³⁴ This probably led to an increase in water intake that mitigated large increases in serum Na. When these agents are more widely used in clinical practice, the monitoring of serum Na at the outset of treatment will be very important. The drugs under discussion have short half-lives; therefore, a discontinuation or decrease in dosages will translate into rapid changes in water excretion.

The clinical studies discussed above have specifically avoided the use of the vasopressin antagonists in hypovolemic states. Although hypotension has not been reported as an adverse effect, it could occur in this setting, particularly when the combined V_{1a}/V₂ antagonist is employed. Such an agent can also potentially cause splanchnic vasodilatation leading to an increased risk of bleeding from varices in patients with cirrhosis. In contrast, there is at least a theoretical possibility that the pure V₂ antagonist could be deleterious in heart failure, as the V_{1a} receptor remains unblocked in the face of increasing vasopressin levels. This was not observed in the aforementioned studies,^{32,33} in the SALT

trials,²⁰ or the EVEREST trial.³⁴ It is hoped that the results of the EVEREST trial³⁴ will provide the requisite information on this issue. Finally, drug interactions, particularly with drugs metabolized by the CYP344 pathway, will have to be considered, but with the exception of conivaptan, this does not appear to pose a serious clinical problem.

Summary and unanswered questions

The development of the vasopressin antagonists (vaptans) and their advent into clinical practice clearly portend a new era in the treatment of hyponatremic disorders. By addressing the primary mechanism that underlies these disorders, these agents provide the most physiologic of approaches to the enhancement of free water excretion and the correction of electrolyte abnormalities. At present, only an IV form of a V₂/V₁ antagonist is available for euvolemic and hypervolemic conditions such as the SIADH and CHF, respectively. The aquaretic agents provide a reliable, predictable, yet not excessive, increase in serum Na concentration without significant attendant changes in Na or K excretion. The use of these drugs also appears to be free of significant adverse effects and they are extremely well-tolerated, allowing patients free water access. Therefore, they possess many of the qualities a clinician would look for in an ideal drug to treat these conditions and they are superior to all of the presently available treatments. However, a number of questions remain that require further assessment and data collection. At this time, it is unclear whether treatment with intravenous conivaptan will suffice for patients with acute symptomatic hyponatremia or whether additional treatment with 3% saline is needed to complement the drug. It is also not known whether the correction of hyponatremia will significantly impact a patient's quality of life, cognitive function, rate of hospitalization, or overall mortality. Finally, an assessment of the value of sole V₂ receptor blockade versus combined V_{1a}/V₂ blockade is of interest, particularly to assess whether V_{1a} blockade adds to the effects of beta-adrenergic, renin-angiotensin, and aldosterone blockade in patients with advanced cardiac disease. Clearly, further clinical trials directed at providing answers to these unanswered questions are still needed.

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31 October – 5 November 2007

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