Vaptans: A new option in the management of hyponatremia

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Abstract

Arginine vasopressin (AVP) plays an important role in water and sodium homeostasis. It acts via three receptor subtypes—V_1a, V_1b, and V_2—distributed widely throughout the body. Vaptans are nonpeptide vasopressin receptor antagonists (VRA). By property of aquaresis, VRAs offer a novel therapy of water retention. Conivaptan is a V_1a/V_2 nonselective VRA approved for euvolemic and hypervolemic hyponatremia. Tolvaptan is the first oral VRA. Other potential uses of this new class of drugs include congestive heart failure (CHF), cirrhosis of liver, syndrome of inappropriate secretion of antidiuretic hormone, polycystic kidney disease, and so on. These novel drugs score over diuretics as they are not associated with electrolyte abnormalities. Though much remains to be elucidated before the VRAs are applied clinically, the future holds much promise.

Key words: Aquaresis, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, vaptan, vasopressin receptor antagonists

Introduction

Hyponatremia, one of the most common electrolyte abnormalities in hospitalized patients, is defined as serum sodium concentration <135 mEq/L. Its prevalence is one in five of all hospitalized patients.[1] Recent clinical data suggests that hyponatremia is not only a marker of disease severity but also contributes to the diseases independently.[2-4]

About 85–90% of all sodium is extracellular; therefore, extracellular fluid volume (ECF) is a reflection of the total sodium content in the body. Hyponatremia usually reflects retention of excessive water relative to sodium rather than sodium deficiency alone.[5-9]

Mechanisms of osmoregulation and volume regulation help to maintain water balance and tonicity in the body. Interplay of the renal action of arginine vasopressin (AVP) or antidiuretic hormone (ADH), renin angiotensin aldosterone system (RAAS), sympathetic nervous system (SNS), and thirst help to control water homeostasis in the body and keep plasma osmolality between 275 and 290 mOsm/kg water.

Hyponatremia can be associated with low, normal, or high tonicity. Tonicity refers to osmolytes that are impermeable to the cell wall.[4,5] Isotonic hyponatremia refers to the expansion of ECF with isotonic fluids that do not contain sodium (e.g., mannitol). Hypertonic hyponatremia occurs when there is increase in effective osmoles in ECF with shift of water from the cells to ECF (e.g., hyperglycemia in insulin-resistant states) called translocational shift. Hypotonic hyponatremia is the most common form of hyponatremia and occurs either due to impaired renal excretion of water or excess intake of water in the presence of normal renal excretion.

Hypotonic hyponatremia is of three types depending on the ECF volume associated with it—hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia.[9] Hypovolemic hyponatremia is characterized by low serum sodium associated with contraction of plasma volume, signs of dehydration, and prerenal failure along with lack of edema and ascites.[9,10] Physical examination shows tachycardia, orthostatic hypotension, and flat neck veins. In euvolemic hyponatremia, there is relative gain of water due to impaired water excretion combined with increased intake. Physical examination reveals absence of features of

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ECF overload (e.g. edema, ascites, pulmonary edema) or ECF volume depletion (tachycardia, low blood pressure, flat neck veins). The most common cause of euvolemia is syndrome of inappropriate ADH secretion (SIADH).[11] Hypervolemic hyponatremia is due to expanded ECF volume and plasma with ascites and edema. There is disproportionate renal retention of water with respect to the retention of sodium.

Brain Adaptation in Acute and Chronic Hyponatremia

When ECF sodium decreases below normal values, water moves into the cells to attain the osmotic balance causing cell swelling. To limit this change in homeostasis and prevent cerebral edema, brain cells extrude solutes like potassium followed by organic osmolytes (*myo*-inositol, glutamine, choline, taurine). Prevention of cerebral edema by this adaptive process depends on the severity of hyponatremia, rate of reduction of serum sodium concentration, and so on.

During recovery, when serum sodium concentration returns to normal, electrolytes correct quickly in brain cells but correction of organic osmolytes is slow.[12,13] Here, overzealous treatment (>1 mEq/L/h) will outpace the ability to recapture lost organic osmolytes leading to intracellular depletion of water. This causes shrinkage of cells, myelinolysis, and a condition called osmotic demyelination syndrome (ODS) characterized by flaccid paralysis, dysarthria, and dysphagia. The consensus is that correction of chronic hyponatremia should be <12mmol/L in 24 hours or <18mmol/L in 48 hours.[7]

Role of Vasopressin

AVP is a neuropeptide hormone synthesized by two hypothalamic nuclei (supraoptic nuclei and paraventricular nuclei) and secreted by the posterior pituitary in response to an increase in plasma tonicity or decrease in plasma volume.[14] Some nonosmotic factors also regulate the secretion of AVP, such as effective circulating (arterial) volume, nausea, pain, stress, hypoglycemia, pregnancy, and drugs.

The actions of AVP are mediated by three receptor subtypes: V_1a, V_1b, and V_2. All of them are G protein-coupled receptors and are identified by their location, second messenger systems, and effects [Table 1].

V_1a receptors are present on vascular smooth muscle cells, myocardium, platelets, and hepatocytes, and mediate vasoconstriction, platelet aggregation, and glycogenolysis. They may also be mediators of myocyte hypertrophy.[14-16] V_1b receptors have little selective distribution in the central nervous system (CNS). V_2 receptors are expressed in principal cells of the renal collecting duct system. They mobilize intracellular vesicles of aquaporin 2 to the apical plasma membrane of collecting duct cells causing an increase in the reabsorption of free water. AVP acts on V_2 receptors on the basolateral surface of principal cells resulting in activation of adenylyl cyclase. This leads to protein kinase activation resulting in preformed cytoplasmic vesicles called aquaporins getting inserted into the luminal membrane. They span the luminal membrane and permit movement of water down an osmotic gradient. The water absorbed is returned to the systemic circulation across the basolateral membrane. When the effect of AVP has worn off, water channels are removed from the luminal membrane by endocytosis, aggregate within clathrin-coated pits, and are returned to the cytoplasm [Figure 1].[6,14]

It may be noted that the stimulation of V_1a receptors occurs at plasma concentrations of AVP greater than those needed for V_2-dependent antidiuretic effect. This differential sensitivity has been attributed to differential amplification of the signal transduction pathway.[14] V_1 receptors stimulate prostaglandin synthesis by medullary interstitial cells. This action may offset or counterbalance V_2 receptor-mediated antidiuresis.

Orally and intravenously active nonpeptide vasopressin receptor antagonists (VRAs) are called vaptans. They cause aquaresis, that is, excretion of solute-free urine. They differ from the diuretics as they promote excretion of water without the loss of electrolytes and hence are categorized as aquaretics. Peptide antagonists are associated with crucial drawbacks—they can be used parenterally only; when given chronically, they showed a paradoxical agonistic effect.[14] Nonpeptide VRAs are orally active [Table 2].

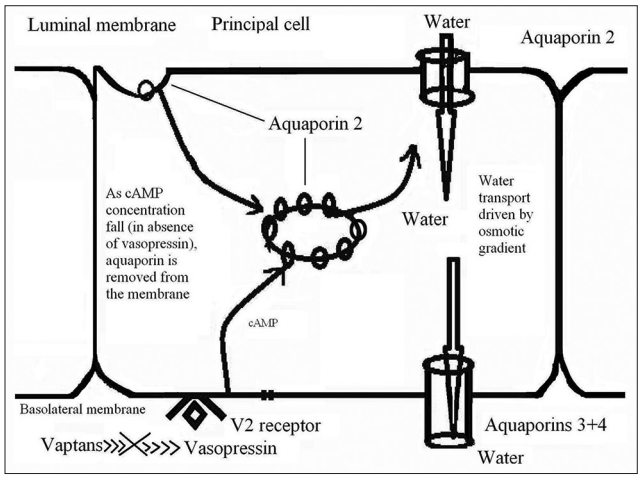

Figure 1: Aquaporin-mediated water transport in the renal collecting duct and site of action of vaptans[6]

Table 1: Subtypes of vasopressin receptors, their location, and function[15]

Receptor (2nd messenger)	Location	Function/effects
V_1a (G-protein IP_3, Ca^{2+})	Vascular smooth muscle Platelet	Vasoconstriction, myocardial hypertrophy Aggregation
	Hepatocytes	Glycogenolysis, urea synthesis
	Myometrium	Uterine contraction
	Renal	Stimulation of prostaglandin synthesis, decrease in inner renal blood flow, glomerular mesangial contraction
	Adrenal	Stimulation of aldosterone and cortisol secretion.
	Brain	Memory, stress adaptation, social recognition, circadian rhythmicity, temperature regulation, regulation of blood pressure and heart rate
V_1b (G-protein IP_3, Ca^{2+})	Pancreas	Insulin release
	Brain corticotroph cells of anterior pituitary	Stress adaptation ACTH release/β-endorphin release
V_2 (G-protein, adenyl cyclase, cAMP)	Basolateral membrane of renal collecting tubule	Free water resorption
	Pneumocytes, type 2	Stimulation of sodium resorption (through activation of epithelial sodium channel)
	Vascular endothelium	Releases von Willebrand factor and factor VIII
	Vascular Smooth muscle	Vasodilatation

ACTH: Adrenocorticotropic hormone; cAMP: Cyclic adenosine monophosphate; IP3: Inositol triphosphate; Ca2+: Calcium

Table 2: Oral and parenteral nonpeptide antagonists in clinical development and their potential clinical uses[15]

Receptor	Nonpeptidea antagonist	Potential uses
V_1a	Relcovaptan (OPC-21268)	Raynaud's syndrome,[17] dysmenorrhoea, preterm labor,[18] ACTH-independent macronodular adrenal hyperplasia
V_1b	Nelivaptan (SSR-149415)	Depressive disorders[19]
V_2	Lixivaptan (VPA-985)	Hyponatremia (SIADH, cirrhosis,[20] CHF[21,22])
	Tolvaptan (OPC-41061)	Hyponatremia CHF, polycystic kidney disease
	Mozavaptan (OPC-31260)	Hyponatremia (only SIADH)
	Satavaptan (SR-121463)	Hyponatremia, CHF, cirrhosis
$V_{1a}+V_2$	Conivaptan	Hyponatremia, CHF

ACTH: Adrenocorticotropic hormone; CHF: Congestive heart failure; SIADH: syndrome of inappropriate antidiuretic hormone secretion

Clinical Experience with Vaptans in Hyponatremia

Studies of Ascending Levels of Tolvaptan (SALT-1 and SALT-2) were designed to focus specifically on changes in serum sodium in patients with hyponatremia from multiple disorders including SIADH, heart failure, and cirrhosis.[23] The studies enrolled 205 and 243 patients, respectively. The patients received daily oral doses of either placebo or tolvaptan 15 mg with titration to 30 and 60 mg four times a day (as needed) to correct sodium over 30 days, with a follow-up visit seven days after the end of the study. Primary endpoints were average change in serum sodium from baseline to day 4 and day 30 of treatment.

In SALT-1, patients receiving tolvaptan had an average daily area under curve (AUC) change in serum sodium by day 4 of 3.62 ± 2.68 mEq/L as compared to 0.25 ± 2.08 mEq/L in the placebo group ($P < 0.0001$). At day 30, this averaged 6.22 ± 4.10 for tolvaptan and 1.66 ± 3.59 mEq/L for placebo ($P < 0.0001$). The results of SALT-2 were similar. In both studies, serum sodium improved more in the tolvaptan-treated patients. The tolvaptan group of patients required less restriction of fluids and it was superior to placebo in raising and maintaining serum sodium concentration.

However, during the seven-day follow-up period (after stopping tolvaptan), hyponatremia was again observed, indicating that the continued aquaretic effect of tolvaptan was required to maintain normal sodium concentrations in patients with chronic hyponatremia, although long-term studies do not support this.[24]

Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER) was an open-label extension of the earlier SALT study in which the SALT enrollees who previously received either tolvaptan or placebo for 30 days were given oral tolvaptan for up to 804 days.[25] A total of 111 individuals participated in SALTWATER, of whom 64 discontinued the drug, 30 because of death or adverse reactions. At 50 weeks, the serum sodium concentration normalized in approximately 60% of the patients.

Adverse effects of vaptans

VRAs are a group of well-tolerated drugs. The most common side effects observed are thirst, pollakiuria (increased daytime urination), and dry mouth. In randomized double-blind studies, thirst was reported as a side effect in 29% patients.[13,25] Aquaretics increase thirst by increasing blood tonicity and

urine volume leading to resetting of osmostat. This secondary thirst could increase intake of fluids and jeopardize the therapeutic effect.

Hypernatremia due to markedly negative fluid balance was observed uncommonly (2–4% patients) in short-term studies. Rebound hyponatremia may occur after withdrawal due to a compensatory rise in plasma AVP levels. This upregulated AVP may increase retention of water and offset the therapeutic benefit obtained. A rapid rise in serum sodium concentration can lead to neurological sequelae. A rise of serum sodium >8 mmol/L within the first few days was seen in 4–14% patients.[13] So far, no study has reported central pontine myelinolysis.

Studies have shown an increased incidence of hypokalemia with conivaptan.[16] It induces loss of potassium via enhanced urinary flow and facilitates the secretion of potassium at collecting tubules. Renal failure due to depletion of intravascular volume (hypotension) is another area of concern. However, no significant impairment of renal function has been observed. Orthostatic hypotension has been reported infrequently.[26]

In a study by Konstam *et al*.,[22] the most frequent adverse effects were thirst, nausea, hypotension, constipation, dizziness, and dry mouth. Hypernatremia occurred in 1.7% of the tolvaptan-treated patients compared with 0.5% of the placebo patients. Discontinuation of the drug due to adverse effects occurred in 6.5% of the tolvaptan patients and 5.5% of the placebo patients.

In a conivaptan study group, incidence of deaths, serious adverse events, and discontinuation for any reason were comparable among patients who were given either conivaptan or placebo.[27] Most common adverse effects were injection site phlebitis, hypotension (pharmacodynamic effect), pyrexia, hyperkalemia, and injection site thrombosis.

In laboratory animals, conivaptan exerted fetopathic effects at doses that were less than the therapeutic dose. It delayed labor in rats at doses that were equivalent to their therapeutic doses.[28,29] Conivaptan has been placed in Pregnancy Ccategory C by the United States Food and Drug Administration (USFDA).

Coadministration of conivaptan can increase plasma concentrations of midazolam, simvastatin, digoxin, and amlodipine. Conivaptan is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), which could lead to serious drug-drug interactions. Tolvaptan has less potential for drug-drug interactions.[30] Coadministration of conivaptan with potent inhibitors of (CYP3A4), such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated. Because of this drawback, oral preparation of conivaptan has not been developed.[15]

Most of the studies so far have been for short periods and under strict clinical and analytical surveillance using low doses of diuretics; therefore, study results under different conditions (high doses of diuretics, long term) need to be evaluated to observe the entire spectrum of adverse effects.

Management of Hyponatremia

Current approaches to the treatment of hyponatremia are suboptimal, have variable efficacy, have slow responses, are poorly tolerated, and have important undesirable side effects.[11] Treatment is guided by the patient's volume status, duration, and magnitude of hyponatremia, and degree and severity of clinical symptoms [Table 3].[31]

Treatment of the three types of hypotonic hyponatremia and the role of vaptans in each of them is discussed below.

Hypovolemic hypotonic hyponatremia

Intravenous hypertonic saline corrects the deficiency of sodium responsible for hyponatremia as well as produces a solute diuresis that serves to remove some of the excess water. The rate of infusion should be less than 0.05 mL/kg/minute. Serum sodium should be monitored two hourly. Infusion should be stopped as soon as serum sodium increases by 12 mmol/L or to 130 mmol/L, whichever is first.[7,9,32]

Vaptans are contraindicated in hypovolemic hyponatremia as these individuals already have a large deficit of water and sodium that compromises hemodynamic stability and renal function.[16]

Euvolemic hypotonic hyponatremia

Restriction of dietary water to 0.5–1L/d is the mainstay of treatment. In SIADH, isotonic saline represents a source of free water and should not be used. Hypertonic saline with or without loop diuretics is advocated for the correction of hyponatremia in severe cases. In addition, the rate of correction should be adjusted to increase serum sodium concentration by no more than 1–2 mEq /L/hour and not more than

Table 3: Clinical features of hyponatremia at different plasma concentrations

Plasma concentration (mEq/L)	Signs/symptoms
130-135	Asymptomatic
125-130	Nausea and malaise
115-120	Headache, lethargy, disorientation
Severe and rapidly developing	Seizure, coma, permanent brain damage, respiratory arrest, brainstem herniation, and death

25–30 mEq/L in the first two days.[7,9,32] The underlying cause for SIADH should be eliminated. Demeclocycline (300–600 mg twice daily) may be used for those who cannot adhere to restriction of water. Fludrocortisone (0.05–0.25 mg twice daily) is used in cases of cerebral salt-wasting syndrome.

Mozavaptan has been approved in Japan for paraneoplastic SIADH, and the European Medicines Agency (EMEA) has approved tolvaptan specifically for the treatment of adult patients with hyponatremia secondary to SIADH. Conivaptan has been used in dilutional hyponatremia associated with hypothyroidism, renal dysfunction, and malignancies. A study with other vaptans (satavaptan) has also been encouraging.[14] A recent publication[32] indicated that severe acute hyponatremia (<118 mmol/L) might become an indication for vaptan treatment, citing two reasons—greater ease in terms of titrating the correction rate of hyponatremia with vaptan than with hypertonic saline, and no risk of pulmonary edema in response to vaptan as opposed to hypertonic saline.

Hypervolemic hypotonic hyponatremia

This category commonly comprises patients of congestive heart failure (CHF) and cirrhosis. In CHF, hyponatremia is associated with increased mortality and increased rate of rehospitalization in patients of acute heart failure.[33,34] Restriction of water and treatment of the underlying condition along with the use of diuretics are followed. Nonjudicious use of diuretics can cause electrolyte abnormalities and worsening of kidney function with no survival benefit.

A combined V_1a/V_2 blocker (conivaptan) and a V_2 blocker (tolvaptan) are both available and choice between the two is debatable. In CHF, AVP is upregulated and induces cardiomyocyte hypertrophy and vasoconstriction via V_1a receptor along with enhanced renal water retention via V_2 receptor, as compensatory mechanisms to increase the effective arterial volume. V_1a stimulation is also associated with mitogenic and possibly platelet aggregative effects; therefore, its inhibition can be potentially beneficial for patients with CHF with concomitant hypertension and atherosclerotic disease.[16]

Theoretically, the unopposed action of V_1a by using V_2 blocker alone could lead to coronary vasoconstriction and vagus-mediated myocardial depressant effect. However, tolvaptan has failed to show any adverse cardiac effects, either on blood pressure or heart rate.[15]

Short-term trials like EVEREST (Efficacy of Vasopressin antagonist in hEart FailuRE outcome Study with Tolvaptan) and ACTIV in CHF (Acute and Chronic Therapeutic Impact of Vasopressin antagonist in Congestive Heart Failure) showed a rapid increase in serum sodium secondary to increase in urine output but despite showing improvement in hemodynamic parameters like pulmonary capillary wedge pressure (PCWP)—a clinical indicator of preload, improvement in clinical status was not significant, reflecting that improvement in hyponatremia is not an index of improvement in clinical outcome. Similarly, long-term trials have failed to demonstrate a favorable effect on morbidity and mortality.[35] Moreover, strict monitoring of serum sodium is discomforting for the patient.

In cirrhosis, treating hyponatremia is a prudent step because it helps reduce the frequency and severity of complications such as encephalopathy.[13] Studies with vaptans support the short-term administration of vaptans (up to 1–2 weeks) and have shown a significant improvement of the low levels of sodium.[13] Short-term studies have also demonstrated a reduction in ascites volume.[36] A study with V_2 blocker satavaptan observed that improvement in serum sodium concentrations obtained after the first few days of therapy was maintained for up to one year.[37]

In contrast, the effects derived from V_1a inhibition can be harmful for hypotensive patients or cirrhotic patients with dilated splanchnic beds and variceal bleeds. Further, dilatation of the splanchnic bed and interference with platelet aggregation by V_1a inhibition could exacerbate complications of variceal bleeding. Hypothermia due to skin vasodilatation is another theoretical concern amongst those at risk.[16]

Current Status of Vaptans

Vaptans are the most appropriate physiological approach to treat hyponatremia as they do not deplete electrolytes and can spare the stringent and inconvenient restriction of fluids. They do not stimulate the neurohormonal system and cause no renal impairment. Vaptans can help to decrease the dose of diuretics in CHF.

However a lack of consistency for correction of serum sodium by vaptans has been observed in trials.[16] Moreover, the follow-up treatment is not well defined, for example, conivaptan is given as an intravenous infusion for four days; after this schedule, there are no recommended doses. Its property of inhibition of CYP can cause drug-drug interaction. Despite weaker interactions, tolvaptan is still contraindicated with strong CYP3A4 inhibitors and the drug may be less effective when used with potent CYP3A4 inducers such as rifampin. Reductions in dose should be considered when tolvaptan is used with P-glycoprotein inhibitors such as cyclosporine.[24] Dual blockers (V_1a/V_2) may cause bleeding complications.[16]

Vaptans should not be used to treat the type of euvolemic hyponatremia caused by emetic stimuli or secondary adrenal insufficiency, and they are ineffective in the vasopressin-independent form of SIADH (caused by an activating mutation of the V_2 receptor). They are ineffective where AVP levels are appropriate, for example, cerebral salt wasting and psychogenic polydipsia. Moreover, their effect on the vascular endothelium is unknown. Studies in the pediatric population are also lacking. Their high cost is another factor to be considered.

Conclusion

Loss of sodium along with depletion of volume serves as a signal for the release of AVP. As a result of AVP-stimulated retention of water, blood sodium becomes diluted and hyponatremia results. VRAs are clearly the most exciting addition to the existing armamentarium for the treatment of hyponatremia.

Antagonism of V_1a receptor in vascular smooth muscle cells results in vasodilatation, and antagonism of V_2 receptors in the renal collecting duct results in aquaresis. Intravenous conivaptan, a combined V_1a/V_2 receptor antagonist, has been approved for the treatment of euvolemic and hypervolemic hyponatremia. Tolvaptan, an oral V_2 receptor antagonist is being evaluated for the treatment of hyponatremia in heart failure. Future indications of vaptans are likely to increase.

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