Vasopressin Antagonists: Role in the Management of Hyponatremia

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Hyponatremia · Vasopressin · Salt-water balance · Sodium · Syndrome of inappropriate secretion of antidiuretic hormone · Antidiuretic hormone · Homeostasis

Abstract
Hyponatremia is a common electrolyte disorder associated with potentially serious or life-threatening consequences. Serum osmolality and sodium concentration [Na⁺] are regulated by thirst, the hormone arginine vasopressin (AVP), and renal water and sodium handling. Hyponatremia is frequently caused by dysregulation of AVP, which accompanies disorders of water retention, such as congestive heart failure (CHF) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Clinical trials with AVP receptor antagonists have confirmed the important role of AVP in the pathophysiology of hyponatremia and suggest these agents are efficacious in treating hyponatremia associated with SIADH, cirrhosis, and CHF. Acting directly at AVP receptors in the renal tubules, these agents promote aquaresis – the electrolyte-sparing excretion of free water – in patients with hyponatremia. In clinical trials, AVP receptor antagonists have been shown to increase the serum [Na⁺] and urine output while decreasing urine osmolality.

Introduction
Hyponatremia, defined as a serum sodium concentration ([Na⁺]) less than 136 mEq/l, is the most common electrolyte disorder in hospitalized patients [1]. The disorder may be evident on admission as a complication of underlying disease or it can occur during hospitalization. The reported prevalence of hyponatremia varies depending on the definition of hyponatremia used and the population studied. For example, the prevalence of hyponatremia among hospitalized patients when the disorder is defined as a serum [Na⁺] < 134 mEq/l is 15% and ranges from 3 to 15% when the disorder is defined as a serum [Na⁺] < 130 mEq/l [2–4]. The prevalence of hyponatremia also increases with age [5]. The probability of hyponatremia developing during hospitalization is more than twice as high among people aged 51–60 years than among those aged 30 years and increases about 5-fold in people older than 70 years [5].

Hyponatremia can be a contributing factor to morbidity and death in hospitalized patients. A retrospective analysis of 78 hospitalized patients with a serum [Na⁺] ≤ 128 mEq/l showed that the mortality among these patients was 27% [6]. Furthermore, in a prospective study with 1,088 postoperative patients, hyponatremia (serum [Na⁺] < 130 mEq/l) developed in 4.4%. Among these pa-
patients, the mortality was 4.2%, compared with 0.2% among patients who did not have hyponatremia or did not undergo serum [Na+] measurements. In a study of 4,532 patients aged 65 years or older, the risk of death among patients with hyponatremia (serum [Na+] <130 mEq/l) at admission was twice as high as that among patients in the same age group who did not have hyponatremia at admission (16 vs. 8%, respectively) [7].

Most significant sequelae of hyponatremia result from its effects on the central nervous system. Hyponatremia carries a significant risk of permanent brain damage or death from encephalopathy. The magnitude and duration of hyponatremia were once believed to predict the risk of hyponatremic encephalopathy, but age, sex, and hormonal status are now believed to be the more prominent risk factors. Although the incidence of hyponatremia is similar among men and women, brain damage occurs predominantly in younger menstruant women and in preadolescents of either sex [8]. Hypoxia impedes compensatory changes in the brain as it tries to adapt to hyponatremia and stimulates the antidiuretic hormone arginine vasopressin (AVP). Hypoxia can also lead to permanent brain damage and death. The risk of respiratory arrest in patients with symptomatic hyponatremia is much greater than that in patients who receive inappropriate treatment [8].

Serum sodium is the principal solute governing serum osmolality, which is determined by the total solute concentration in a fluid compartment [9]. The balance between sodium and water is maintained as needed by increased water intake (thirst) during periods of hyperosmolality or by increased renal free water clearance (FWC) during periods of hypoosmolality. The major regulatory factor in the maintenance of total body volume is AVP. Both thirst and AVP release are stimulated by hypertonicity. Tonicity describes the collective ability of all solutes in a compartment to create an osmotic gradient for net water movement between compartments. Tonicity will therefore increase when the extracellular [Na+] rises. Impaired regulation of AVP leads to a disruption in water balance, resulting in hyponatremia.

Current therapeutic approaches to hyponatremia produce variable and often disappointing results because they do not address the underlying etiology or effects of AVP dysregulation. AVP receptor antagonists, a new class of drugs for the treatment of hyponatremia, act on AVP receptors in the renal tubules to promote aquaresis – the electrolyte-sparing excretion of water – and subsequently increase the serum [Na+].

**AVP in Normal and Dysregulated Water Handling**

**AVP Release: Osmotic and Nonosmotic Stimuli**

AVP is a 9-amino acid peptide hormone that is synthesized by neuronal cell bodies in the hypothalamus. AVP-carrying neurosecretory granules travel down the supraoptic hypophyseal tract and are stored in the posterior pituitary [10, 11]. In response to the appropriate trigger, their release occurs quantally by exocytosis from the granules [12].

The control of AVP release is governed by both osmotic and nonosmotic stimuli, with changes in osmolality serving as the primary stimulus for hormone release. AVP release is controlled through an exquisitely sensitive system that detects extracellular fluid (ECF) osmolality. Two unique groups of osmoreceptors in the hypothalamus detect ECF osmolality. One group of relatively high-threshold receptors stimulates thirst when plasma osmolality reaches approximately 288–294 mosm/kg [13, 14]. The other group of osmoreceptors signals water reabsorption at the kidney by triggering AVP release if the ECF exceeds the osmolality set-point, which is usually 280 mosm/kg [9]. The relationship between AVP release and increasing osmolality is linear and steep beyond the set-point [13].

The exact threshold for AVP release declines with age and during pregnancy [15, 16]. The slope of the osmolality-AVP response is also modified in relation to increases and decreases of blood volume and pressure. In the healthy individual, the renal response to AVP is also linear, and a decrease in urine flow and accompanying increase in urine osmolality will follow in proportion to the systemic AVP level [14].

In patients with inappropriate AVP regulation, the balance between osmolality and water reabsorption can be lost by dysregulation of the intensity or duration of AVP release. In some cases, the osmoreceptor set-point can be disturbed, resulting in the inappropriate release of AVP despite normal osmolality. In the syndrome of inappropriate antidiuretic hormone (SIADH), for example, the AVP level may be disproportionately elevated in relation to the tonicity of body fluids.

In contrast with the intricate control of water reabsorption directed by the osmoreceptor, nonosmotic AVP release is relatively insensitive. A decrease in the effective arterial volume of approximately 10% is necessary to trigger AVP release [9]. Unlike the direct linear relationship with osmolality, the relationship between volume depletion and AVP release is curvilinear. The release of AVP may also be stimulated by nausea, pain, and medications,
such as chlorpropamide, carbamazepine, clofibrate, vincristine, and cyclophosphamide [13].

**Classification of Hyponatremia**

**Volume Status**

In patients with hyponatremia, the disorder may be hypovolemic, euvolemic, or hypervolemic (table 1), depending on their extracellular volume status, which is determined from the medical history, daily fluid input and output measurements, and physical examination [17].

Hypovolemic hyponatremia begins when volume is decreased by conditions such as diarrhea, vomiting, diuretic use, or excessive sweating, all of which lead to the loss of both sodium and water. When the extracellular loss is reversed with hypotonic fluids, such as oral free water, the net sodium loss is disproportionally greater than water loss, which can lead to hypovolemic hyponatremia [18]. Furthermore, AVP secretion is increased as part of the compensatory response to defend against volume contraction, which increases water reabsorption and further decreases ECF osmolality.

Hypervolemic states such as congestive heart failure (CHF), cirrhosis, and nephrotic syndrome are associated with an increased ECF volume and dilution of electrolytes [19]. In these volume-expanded states, the effective intravascular circulating volume is diminished, resulting in poor renal perfusion. The kidney will retain sodium and water avidly even as the total body water and sodium are increased. In these edematous states, hyponatremia occurs when total body water increases more than sodium. Much of the increased body water is due to an elevated AVP level [18].

Euvolemic hyponatremia occurs in patients with normal or near normal ECF volume. SIADH represents the most common form of euvolemic hyponatremia among hospitalized patients. Patients with SIADH usually do not demonstrate any clinical signs of edema, because only a portion of the retained fluid is distributed in the ECF [20]. In SIADH, AVP levels are elevated and the kidneys retain free water, but sodium handling remains intact. The cardinal features of SIADH include (1) hypoosmolar hyponatremia, (2) continued renal excretion of sodium, (3) the absence of clinical evidence of volume depletion, (4) inappropriate urine osmolality (i.e., less than maximally dilute urine), and (5) normal renal and adrenal function [21].

It is often difficult to differentiate between subtle volume depletion and euvolemic hyponatremia, particularly in the absence of clear indicators of hypovolemia, such as orthostatic hypotension. Measurement of urine sodium and response to saline infusion may help to make a precise diagnosis (table 1) [18]. Low [Na⁺] in the urine suggests decreased volume; in contrast, SIADH usually results in an increased urine [Na⁺]. It is important to differentiate mild or early-onset hyponatremia from euvolemic hyponatremia. For example, hyponatremia occurring after neurosurgery may be caused by SIADH or cerebral edema.
Hyponatremia

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salt wasting syndrome, both of which have a similar clinical presentation. An accurate diagnosis of the type of hyponatremia that occurs in patients who have undergone neurosurgery is critical because the treatment of each condition differs substantially, and the wrong approach can be potentially dangerous [22].

Rate of Onset

The symptoms of hyponatremia vary and are dependent on the rate of onset. Acute hyponatremia (onset <48 h) can result in coma, irreversible neurologic damage, respiratory arrest, brainstem herniation, and death [23]. Symptoms are more severe in acute hyponatremia because the brain cannot adapt rapidly to the change in serum [Na⁺]. Chronic hyponatremia (onset >48 h) produces more subtle symptoms, including lethargy, nausea, headache, and disorientation. In this case, the brain can compensate for falling serum [Na⁺] through the excretion of organic solutes that promote water loss and ameliorate brain swelling. This adaptation can minimize the risk of symptoms during chronic hyponatremia, but it may also lead to osmotic demyelination in association with rapid sodium correction [23].

Therapeutic Approaches to Hyponatremia

There is currently little consensus on the treatment of hyponatremia, and evidence-based guidelines are lacking. Fluid restriction is recommended as first-line therapy for the treatment of euvolemic hyponatremia, but its efficacy is unproven. This strategy is frequently impractical, particularly when restriction to less than 1 liter/day is required, and it causes inconvenience and discomfort to patients [20, 24]. Demeclocycline has been recommended as second-line therapy, but it produces poor results and troublesome adverse events, including azotemia, photosensitivity, and nausea. It is also contraindicated in cirrhosis or renal failure [13, 25].

It is generally agreed that active treatment of symptomatic hyponatremia is necessary regardless of the disorder's etiology or rate of onset. After the underlying cause, if known, is eliminated, sodium replacement is effective in patients with symptomatic hyponatremia. In these patients, serum [Na⁺] must be monitored closely. In patients with acute symptomatic hyponatremia, hypertonic saline (3%) should be administered at a rate of 1–2 ml/kg per h. In cases of volume overload, a loop diuretic should be administered. In patients with symptomatic chronic hyponatremia, the overall serum [Na⁺] should not be increased by more than 12 mEq/l over the first 24 h, because rapid correction can produce osmotic demyelination and significant permanent neurologic deficits [13].

In patients with chronic hyponatremia, the brain adapts by depleting osmolites to avoid swelling. As a result, hyponatremia with slow onset may be relatively asymptomatic, even if severe. In such patients, overly rapid correction of sodium can produce central pontine myelinosis. The neurologic symptoms of pontine myelinolysis usually do not appear until several days after sodium administration and are irreversible [26]. Since current treatment strategies do not produce a predictable response, frequent monitoring is necessary to reduce the associated risks.

AVP Receptors

There are three distinct receptor subtypes that bind AVP and confer biologic activity at the target organ: the V₂ receptors, which are found primarily in the kidney, the V₁A receptors, which are expressed in vascular smooth muscle cells and in the heart, and the V₃ receptors, which are found primarily in the anterior pituitary [27, 28]. Less is known about the specific mechanisms of signal transduction pathways involving V₃, which has a profile distinct from that of V₁A and V₂.

The physiologic action of AVP on water balance results from its binding to the V₂ renal receptor. The V₂ receptor is a G-protein-coupled receptor found on the basolateral membrane of the collecting duct. When bound to ligand, V₂ acts through the Gα₂ stimulatory protein to increase adenyl cyclase activity to form cyclic adenosine monophosphate, which then activates protein kinase A. As a result, aquaporin-2 is phosphorylated by protein kinase A and mobilized to the luminal membrane, where it transports water from the collecting duct, thus increasing water reabsorption [11, 29]. In normal physiologic states, renal escape from the antidiuretic effect of AVP occurs through the downregulation of aquaporin-2 and V₂ receptor binding in the kidney [30]. During pregnancy, SIADH, CHF, and cirrhosis, this escape mechanism is diminished and aquaporin-2 is chronically upregulated, increasing water retention proportionally with AVP secretion [31–33].

AVP Receptor Antagonism

Early pharmacologic efforts to block AVP at the receptor were focused on modifications of endogenous ligands to produce peptide antagonists [34, 35]. The unfavorable pharmacokinetic and pharmacodynamic properties of

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these peptides precluded further clinical development [28, 36]. The discovery of nonpeptide AVP antagonists through random screening has led to the synthesis of agents with potent antagonist properties against AVP receptors. These agents confirmed the role of AVP in the pathogenesis of hyponatremia and demonstrated the pharmacologic consequences of modifying AVP binding with the V₂ receptor [37]. The development of AVP receptor antagonists has opened new avenues for a pharmacotherapy that addresses the underlying cause of hyponatremia directly.

V₂ Receptor Antagonists

A novel class of nonpeptide agents that demonstrate antagonism against the AVP V₂ receptor have been developed recently. AVP receptor antagonism has been demonstrated to stimulate free water excretion without sodium loss [38]. In animal models, AVP receptor antagonists produced significant aquaretic effects without compensatory activation of the renin-aldosterone-angiotensin system, an undesirable adverse effect of diuretics [39, 40]. Accordingly, specific AVP blockade has been shown to be beneficial in animal models of SIADH, CHF, and cirrhosis [39, 41–44]. The efficacy and tolerability of the V₂ receptor antagonists lixivaptan, tolvaptan, and OPC-31260 have been evaluated in clinical trials.

In a phase 2 study, 60 patients with dilutional hyponatremia (serum [Na⁺] between 115 and 132 mEq/l) secondary to cirrhosis were randomly assigned to receive placebo (n = 20), lixivaptan 100 mg/day (n = 22), or lixivaptan 200 mg/day (n = 18) for 7 days [45]. Both lixivaptan 100 and 200 mg/day produced significantly greater increases in FWC [0.3 ± 0.3 ml/min (p < 0.01) and 1.2 ± 0.4 ml/min (p < 0.001), respectively] than did placebo. Lixivaptan 200 mg/day was associated with increased sodium excretion (from 24 ± 8 mEq/12 h on day 1 to 34 ± 17 mEq/12 h on the final day of treatment). Lixivaptan also increased serum [Na⁺] in accordance with the dosage given, whereas placebo did not. In patients given lixivaptan 100 mg/day, the mean ± SE serum [Na⁺] increased from 128.3 ± 4.1 to 130.4 ± 6.5 mEq/l (p < 0.053), and in those given lixivaptan 200 mg/day, the serum [Na⁺] increased from 126.4 ± 4.4 to 132.3 ± 6.9 mEq/l (p < 0.001). Lixivaptan 200 mg/day was associated with increased thirst [45].

In another phase 2 trial, 44 patients with hyponatremia (serum [Na⁺] <130 mEq/l; 33 patients with cirrhosis, 6 with CHF, and 5 with SIADH) were randomly assigned to receive placebo or daily doses of lixivaptan 25, 125 or 250 mg for 7 days [46]. Lixivaptan therapy produced significantly greater dose-related increases in FWC (p < 0.05) and serum [Na⁺] (p < 0.05) than did placebo, without significant changes in orthostatic blood pressure. Urinary sodium excretion did not increase with lixivaptan therapy. Lixivaptan was generally well-tolerated, but higher doses were associated with increased thirst and excessive diuresis [46].

The role of tolvaptan in patients with CHF has been evaluated in two large-scale studies [47, 48]. The first study, 254 patients with CHF (New York Heart Association (NYHA) class I–III) were randomly assigned to 25 days of treatment with placebo or tolvaptan 30, 45 or 60 mg/day [47]. The primary efficacy variable was the mean decrease from baseline in body weight. All doses of tolvaptan produced significant weight reduction on the first day of treatment (p < 0.001 vs. placebo), but no further reductions were observed during the remainder of the study period. Total urine volume, which was collected only during the first day of treatment, was significantly greater in all three tolvaptan treatment groups (30 mg/day: 3,909 ml; 45 mg/day: 4,232 ml; 60 mg/day: 4,597 ml) than in the placebo group (2,328 ml; p < 0.05). A subset of 70 patients (28%) had hyponatremia (serum [Na⁺] <136 mEq/l) at baseline. At day 1 of treatment, 80% of patients given tolvaptan demonstrated normalization of serum [Na⁺], compared with 40% of patients given placebo (p < 0.05). Normalization of serum [Na⁺] was maintained throughout the study period in 82% of patients given tolvaptan and 40% of those given placebo (p < 0.05) [47].

The second study included 319 hospitalized patients with CHF (NYHA class III–IV) and left ventricular ejection fraction less than 40% [48]. Patients were randomly assigned to receive placebo or tolvaptan (30, 60 or 90 mg/day) for 60 days (up to 10 days of inpatient treatment and then 7 weeks of outpatient treatment). The coprimary efficacy measures included the change in body weight at 24 h after administration of the first dose of study drug (during inpatient treatment) and worsening of heart failure 60 days after randomization (outpatient treatment). Patients given tolvaptan experienced significantly greater weight loss (median reduction, 1.8–2.1 kg) than those who received placebo (0.6 kg; p = 0.002). Urine volume on day 1 was significantly higher in patients who received tolvaptan than in patients who received placebo and remained higher throughout the hospitalization period (fig. 1). The rate of worsening heart failure did not differ between the tolvaptan and placebo groups (26.7 vs. 27.5%; p = 0.88). Baseline evaluations indicated that a subset of 68 patients (21.3%) had hyponatremia (serum [Na⁺] <136 mEq/l). Af-
After treatment with tolvaptan, these patients had a rapid and sustained increase in serum $[Na^+]$ [48].

The efficacy of OPC-31260, the compound from which tolvaptan was derived, was evaluated in 11 patients with hyponatremia ($[Na^+] < 135$ mEq/l) secondary to SIADH [49]. Those who received a single intravenous 0.25 or 0.5 mg/kg dose of OPC-31260 demonstrated both a urine volume 2.1 and 1.9 times, respectively, greater than that in control patients and a lower urine osmolality (<225 mosm/kg). The 0.5-mg/kg dose of OPC-31260 significantly increased serum $[Na^+]$ by about 3 mEq/l at 3 h after administration ($p < 0.01$ vs. serum $[Na^+]$ at baseline) [49]. In a study of 8 patients with cirrhosis who had ascites or peripheral edema (serum $[Na^+]$ was in the normal range), a single 30-mg oral dose of OPC-31260 significantly ($p < 0.01$) increased the urinary excretion rate at 0–2 h after administration and significantly ($p < 0.01$) lowered urinary osmolality at 2–4 h [50]. FWC was also significantly ($p < 0.05$) increased between 0 and 4 h after administration. OPC-31260, however, is no longer in clinical development.

**$V_{1A}/V_2$ Receptor Antagonist**

Conivaptan, a $V_{1A}$ and $V_2$ receptor antagonist, is the first agent in this class to be approved for the treatment of euvolemic hyponatremia in hospitalized patients. In preclinical studies, the aquaretic effect of conivaptan was similar to or greater than that of a loop diuretic, but without the accompanying loss of electrolytes [51, 52].

A phase 3 randomized, double-blind, multicenter, placebo-controlled, parallel-group trial compared the efficacy and tolerability of intravenous conivaptan (a 20-mg loading dose followed by continuous infusion of 40 or 80 mg/day for 4 days) with that of placebo in 85 patients with euvolemic or hypervolemic hyponatremia (serum $[Na^+]$ 115 to $<130$ mEq/l) [53]. Both conivaptan doses produced a significant increase in FWC at day 1 (fig. 2) [54]. Normalization of serum $[Na^+]$ ($\geq 135$ mEq/l) or a $\geq 6$-mEq/l increase from baseline in serum $[Na^+]$ occurred in significantly more patients given either conivaptan 40 mg (69%) or 80 mg/day (88%) than in those given placebo (21%; $p < 0.01$ and $p < 0.001$, respectively). The median time for an increase in serum $[Na^+]$ by 4 mEq/l from baseline was approximately 24 h for both treatment groups ($p < 0.001$) (not estimable for the placebo group).

The safety and efficacy of oral conivaptan have also been evaluated in two additional phase 3 clinical trials that included 83 and 74 patients, respectively, with euvolemic or hypervolemic hyponatremia who were given conivaptan 40 or 80 mg/day or placebo for 5 days [55, 56]. Oral conivaptan produced significant increases in serum $[Na^+]$ ($p < 0.05$) and effective water clearance within the first day of treatment and was well tolerated in patients with hyponatremia. The incidences of drug-related adverse events were comparable among treatment groups. In vivo and in vitro studies indicate that conivaptan is a substrate and potent inhibitor of cytochrome P450 3A4, the liver and small intestine isoenzyme responsible for drug metabolism. Based on these findings, only the intravenous formulation of conivaptan is available for the treatment of euvolemic hyponatremia.
Conclusions

Hyponatremia, a serious electrolyte disorder, occurs most frequently as a complication in the elderly and in patients with SIADH, CHF, or cancer. Until now, the available therapeutic options for treating the various forms of hyponatremia have been limited. AVP receptor antagonism is a novel therapeutic approach involving a new class of pharmacologic agents. The results of clinical studies suggest that the AVP receptor antagonists will promote safe aquaresis through the electrolyte-sparing excretion of free water and correction of serum [Na⁺] in patients with euvolemic or hypervolemic hyponatremia.

References

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