Hyponatremia, Arginine Vasopressin Dysregulation, and Vasopressin Receptor Antagonism

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Abstract
Hyponatremia is often associated with arginine vasopressin (AVP) dysregulation that is regulated by the hypothalamo-neurohypophyseal tract in response to changes in plasma osmolality, commonly in patients with the syndrome of inappropriate antiuretic hormone secretion (SIADH). Potentially lethal complications of hyponatremia most frequently involve the central nervous system and include anorexia, fatigue, lethargy, delirium, seizures, hypothermia and coma, and require prompt treatment. Chronic hyponatremia also complicates patient care and is associated with increased morbidity and mortality, particularly among patients with congestive heart failure. Conventional treatments for hyponatremia (e.g. fluid restriction, diuretic treatment, and sodium replacement) may not be effective in all patients and can lead to significant adverse events. Preclinical and clinical trial results have shown that AVP receptor antagonism is a promising approach to the treatment of hyponatremia that directly addresses the effects of increased AVP and consequent decreased aquareisis, the electrolyte-sparing excretion of free water. Agents that antagonize V2 receptors promote aquareisis and can lead to increased serum sodium. Dual-receptor antagonism, in which both V2 and V1A receptors are blocked, may provide additional benefits in patients with hyponatremia.

Introduction
Hyponatremia is typically defined as a serum sodium concentration ([Na⁺]) below 136 mEq/l and occurs in as many as 6–22% of hospitalized patients. It can be caused by any condition that increases the ratio of total body water to [Na⁺], and it is often associated with arginine vasopressin (AVP) dysregulation. AVP is a polypeptide hormone released from the hypothalamus, or hypothalamo-neurohypophyseal tract, in response to decreases in blood pressure, plasma volume, and/or increases in plasma osmolality. AVP secretion is suppressed when serum osmolality drops below normal. There are two scenarios in which AVP secretion will be sustained, or increased, despite hypo-osmolality. First, when there is dysregulation of cells secreting AVP, which may occur in tumor cells, and is one cause of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Second, when ei-
ther low or high pressure arterial baroreceptors sense decreased effective circulatory volume, their stimulus for AVP secretion will override osmotic signals and result in hyponatremia associated with cirrhosis, congestive heart failure (CHF) and plasma volume depletion.

Potentially lethal complications of hyponatremia most frequently involve the central nervous system (CNS) and include anorexia, fatigue, lethargy, nausea and vomiting, delirium, seizures, hypothermia, and coma. CNS disturbances are usually attributed to acute water disorders but are increasingly being recognized in patients with chronic hyponatremia due to SIADH. Chronic hyponatremia complicates patient care and is associated with increased morbidity and mortality, particularly among patients with CHF, cirrhosis, and nephrotic syndrome. Conventional treatments for hyponatremia (e.g. fluid restriction and diuretic treatment) may not be effective in all patients and can lead to significant adverse events.

Water reabsorption in the collecting duct is mediated by vasopressin activation of type-2 vasopressin (V$_2$) receptors in the basolateral membrane of collecting duct cells. Activation of V$_2$ receptors results in generation of cAMP and activation of protein kinase A (fig. 1) [1, 2]. This results in insertion of aquaporin-2 (AQP2) water channels into the apical membrane of the collecting duct. Once AQP2 is inserted into the apical membrane, H$_2$O enters the cells and then exits via AQP3 and 4 in the basolateral membrane, resulting in transcellular water reabsorption. When the stimulus for H$_2$O reabsorption ends, AQP2 is removed from the apical membrane by endocytosis [1, 2].

Preclinical and clinical trial results have shown that AVP receptor antagonism is a promising approach to the treatment of hyponatremia that directly addresses the effects of increased AVP and consequent decreased aquaresis, the electrolyte-sparing excretion of free water. Agents that antagonize AQP2 promote aquaresis, which results in increased serum [Na$^+$]. Dual-receptor antagonism, in which both V$_2$ and V$_{1A}$ receptors are blocked, may provide additional benefits in patients with hyponatremia secondary to edematous conditions, particularly CHF.

### Clinical Overview of Hyponatremia

Hyponatremia is typically defined as a decrease in serum [Na$^+$] to $<136$ mEq/l [3–7] and is usually due to the inability of the kidney to excrete ingested water. Hyponatremia is characterized, and categorized, by osmolality or the measure of solute (sodium) to kilogram of total body water. Hyponatremia can then be classified into three categories, but we will focus on hypo-osmolar hyponatremia which is the most common form (fig. 2) [5]. Hypo-osmolar hyponatremia can then be stratified by clinical volume assessment. Euvolemic is associated with SAIDH and AVP dysregulation but hypervolemic hyponatremia in the face of CHF, cirrhosis, or nephrosis can be clinically difficult to assess and treat. Under these conditions, low intravascular volume induces water retention through decreased renal blood flow and baroreceptor-mediated increased secretion of AVP, which can worsen the severity of hyponatremia [6, 8].
Fig. 1. Activation of the vasopressin V_{1A} or V_{2} receptor leads to increased protein kinase and stimulation of CREBS thus activating aquaporin-2 (AQP2) channel to allow water (H_{2}O) to pass. This process is mediated via adenylate cyclase-activated cAMP.

Fig. 2. Algorithm for the diagnosis of hyponatremia. BUN = Blood urea nitrogen; HCTZ = hydrochlorothiazide.
Prevalence of Hyponatremia

Hyponatremia is a common electrolyte disorder; its reported prevalence among hospitalized patients is 6–22% [3, 9, 10]. One prospective study indicated that the incidence and prevalence of severe hyponatremia (defined as $[\text{Na}^+] < 125 \text{ mEq/l}$) were 1.5 and 2.6 per 100 hospitalized patients per day, respectively [11]. Another prospective study reported that 30% of patients in intensive care units had hyponatremia [12]. Many hospitalized patients have hyponatremia at the time of admission; in one study, one third of adults with hyponatremia had serum $[\text{Na}^+] < 130 \text{ mEq/l}$ at the time of admission [13]. Hyponatremia is also a frequent consequence of various surgical procedures, including pelvic [14], spinal [15], and pituitary surgery [16].

Hyponatremia is particularly prevalent in the elderly, in part because of an age-related decline in renal function. In a longitudinal assessment of 119 nursing home residents older than 60 years, 53% had at least one episode of hyponatremia during a 12-month follow-up period. The incidence of hyponatremia among these patients was 18%, substantially higher than the 8% for age-matched non-institutionalized persons living in the community [17].

Hyponatremia-Associated Mortality and Morbidity

Hyponatremia is associated with a significantly increased risk of death [4, 18, 19]. In addition, hyponatremia that is not treated promptly and effectively can worsen outcomes among patients with chronic disease, most notably CHF [5]. In one large scale cohort study of 4,123 geriatric patients, the prevalence of hyponatremia on hospital admission was 3.5% (4.6% in women and 2.6% in men), and the in-hospital mortality among that population was 16.0 versus 8.0% among those admitted without hyponatremia. A logistic regression analysis showed that hyponatremia at the time of hospital admission was a significant independent predictor of mortality [20]. In a series of 234 patients admitted to hospital with acute exacerbation of CHF, severe hyponatremia was significantly correlated with an increased risk of death [21]. Similarly, serum $[\text{Na}^+]$ was a primary determinant of survival in a cohort of 203 patients with severe CHF and hyponatremia, among whom the median survival period was significantly shorter (174 days) than that among patients with CHF without hyponatremia (373 days) [22].

Hyponatremia is also associated with a significantly poor prognosis among patients hospitalized for cirrhosis. In one series of 156 patients (191 hospital admissions), the death rate was 26.3% among cirrhotic patients with hyponatremia versus 8.9% among those without hyponatremia [23]. Hyponatremia is also associated with significant morbidity [5, 24] and can produce a wide range of deleterious changes involving almost all body systems, the most important and potentially lethal involving the CNS. Although mild and chronic hyponatremia is often asymptomatic, the symptoms associated with this disorder become more pronounced as serum $[\text{Na}^+]$ decreases. Very low serum $[\text{Na}^+]$ (<125 mEq/l) may produce CNS-related symptoms that include anorexia, fatigue, lethargy, delirium, seizures, hypothermia, and coma. Cheyne-Stokes respiration or respiratory arrest and pathologic reflexes may develop along with worsening cerebral edema in patients with severe hyponatremia. Severe acute hyponatremia can lead to brain-stem herniation, and a rapid drop in serum $[\text{Na}^+]$ to <115 mEq/l can cause sudden death [5, 6]. The treatment of hyponatremia is complex and differs according to its rate of onset [25]. Untreated acute hyponatremia (developing within 48 h) is more likely to cause cerebral edema and neurologic damage than is chronic hyponatremia (developing over 48 h); however, persons with chronic hyponatremia are at risk for osmotic demyelination if the correction of serum $[\text{Na}^+]$ is too rapid [26]. Osmotic demyelination may lead to severe neurologic dysfunction, manifested by quadriplegia, pseudobulbar palsy, seizures, and coma. These symptoms may develop several days after aggressive treatment and are often irreversible [5, 27].

Etiology of Hyponatremia

AVP dysregulation is the most common cause of hypovolemic hyponatremia [13], the prototype being SIADH. Euvolemic hyponatremia associated with SIADH is caused by the aberrant or sustained secretion of AVP in the absence of an appropriate osmotic stimulus (e.g. elevated plasma osmolality). Elevated AVP secretion leads to water retention by the kidney and, in patients with SIADH, AVP secretion is not suppressed when plasma osmolality falls below the normal threshold for stimulation of AVP secretion [28]. This syndrome is particularly common in hospitalized and elderly patients [6]. In one study, for example, 78% of hyponatremic patients in a nursing home population had SIADH [17]. The increased risk for SIADH in older individuals may be related to both increased AVP secretion and changes in renal anatomy and vasculature that occur with age [6].
AVP and Its Role in Water Balance and Blood Pressure Regulation

Serum [Na\(^+\)] is regulated by thirst, AVP, and the renin-angiotensin-aldosterone system (RAAS). AVP is a cyclic nonapeptide hormone synthesized by magnocellular and paraventricular neurons in the supraoptic and paraventricular nuclei of the hypothalamus. It is transported down the pituitary stalk in the axons of these neurosecretory cells and stored in nerve endings in the posterior lobe of the pituitary gland [29]. Release of AVP is triggered by the activation of osmoreceptors in the organum vasculosum of the lamina terminalis or baroreceptor-associated afferents that innervate brainstem neurons that, in turn, project to the hypothalamus [29, 30]. Osmoreceptor-induced AVP release is triggered by increased plasma osmolality, while baroreceptor-induced AVP release is stimulated by either a decrease in blood pressure or relative decrease in blood volume. In response to these stimuli, AVP maintains plasma osmolality through renal free water regulation [31]. Osmotic regulation of AVP is sensitive to a 1–2% change in plasma osmolality, but when low plasma osmolality occurs with low blood pressure, the baroreceptor-mediated release of AVP overrides the suppressive effect of hypo-osmolality. This reaction can exacerbate water retention and worsen hyponatremia.

**AVP Receptors**

The actions of AVP are mediated by three structurally distinct G protein-coupled AVP receptor subtypes (V\(_{1A}\), V\(_2\), and V\(_3\) [or V\(_{1B}\)]) [32, 33]. The V\(_{1A}\) (vascular) AVP receptor is expressed on vascular smooth muscle cells, the myocardium, and platelets and in the liver. At these locations, the receptor activates phosphoinositide pathways that stimulate vasoconstriction, myocardial contraction, platelet aggregation, and glycolgenolysis, respectively [34]. The negative impact of AVP on hemodynamics and cardiac remodeling (e.g. chronic vasoconstriction and vascular hypertrophy) are mediated through the V\(_{1A}\) receptor [31, 35].

The V\(_2\) (renal) AVP receptor is expressed in the vascular endothelium and on cells of the renal distal tubule and collecting duct. This receptor activates cyclic adenosine monophosphate and protein kinase A via Gs and adenylate cyclase to stimulate the release of von Willebrand’s factor from endothelial cells and to increase water permeability, and thus reabsorption, in the collecting duct of the kidney [34]. Permeability is increased by the protein kinase A-mediated synthesis and insertion of AQP2 water channels into the apical membranes of cells lining the collecting duct [32, 36]. Expression of the V\(_2\) receptor may be downregulated in renal cells in response to sustained high levels of AVP. This downregulation is adaptive and helps maintain fluid-electrolyte balance in the presence of chronically elevated AVP [37]. The V\(_3\) (pituitary) AVP receptor (also referred to as the V\(_{1B}\) receptor) is expressed by cells in the anterior pituitary, where it is involved in the regulation of adrenocorticotrophic hormone release through phosphoinositide pathways [32]. The human V\(_3\) receptor is pharmacologically distinct from the V\(_{1A}\) and V\(_2\) receptors [33].

**Aquaporins**

The AQP s are a family of membrane proteins that allow water to pass through biologic membranes. There are 4 major types of renal AQP s located in the distal tubules. Each contains six transmembrane scanning domains forming a central pore that allows water to be reabsorbed from the urine [36]. When AVP binds to the V\(_2\) receptor, the cascade of events previously described results in phosphorylation of regulatory proteins, including AQP2, a water channel in the principal cells of the collecting duct [38]. Upon phosphorylation, AQP2 is inserted into the apical plasma membrane, where it mediates free water reabsorption [36, 37]. This water is then removed to the peritubular capillaries via AQP3- or 4-mediated transport. The removal of AVP from its receptor causes AQP2 to be internalized, which reduces membrane permeability. In normal states, escape from anti-diuresis is accompanied by the downregulation of both AQP and AVP receptors in the kidney [38].

**Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)**

Barter and Schwartz [39] first described criteria for SIADH that are still applicable today: hypotonic hyponatremia, urine osmolality greater than appropriate for the concomitant plasma osmolality, increased natriuresis, absence of edema or volume depletion, and normal renal and adrenal function [40]. SIADH is a relatively common cause of hyponatremia that results from the aberrant or sustained secretion of AVP by the hypothalamic-pituitary system [13, 41]. Elevated AVP secretion leads to renal water retention and extracellular fluid expansion, which is compensated for by increased urinary Na\(^+\) excretion. The combination of water retention and Na\(^+\) excretion leads to hyponatremia. This syndrome develops when there is continued ingestion or infusion of fluids in the presence of persistent antidiuretic activity, almost always due to elevated concentrations of plas-
ma AVP. Patients with SIADH will continue to drink despite having hypotonic hyponatremia, since the inhibitory effect of osmoregulated thirst is not sufficiently strong to stop drinking [7]. Because the regulation of AVP secretion fails in patients with SIADH [28, 41], total body water increases and hypotonic hyponatremia ensues [28].

Osmoregulated AVP release can be measured as plasma AVP in response to infusion of hypertonic saline. This procedure has been used to detect four patterns of AVP dysregulation in patients with SIADH (fig. 2) [7]. The most common (in 40% of patients with SIADH) pattern is the excessive and unregulated release of AVP, which is unrelated to plasma osmolality. In the second most common pattern (~30% of patients), referred to as ‘reset osmostat’, AVP release continues to regulate water excretion at a lower plasma osmolality setpoint. A third pattern is characterized by an inability to stop AVP secretion at low plasma osmolalities, but the osmoregulation of AVP is otherwise normal. In the fourth pattern, the normal osmoregulation of AVP secretion is normal, even as SIADH persists (<10% of patients) [7].

Causes of Hyponatremia

SIADH resulting in hyponatremia may arise in response to a wide range of conditions. Common causes include: cancer that induces ectopic AVP production; HIV/AIDS; pulmonary disease; endocrine disease; neurologic disease or trauma, and surgery (fig. 2) [6, 16, 42]. The synthesis and release of AVP are also chronically elevated in patients with CHF [31]. In advanced CHF, low cardiac output is sensed by baroreceptors that stimulate further AVP secretion to increase vascular resistance and salt/water retention in the kidney [8].

Post Surgical SIADH and Hyponatremia

Hyponatremia, produced by either SIADH or the cerebral salt-wasting (CSW) syndrome, occurs in 9–35% of patients after pituitary surgery, possibly as a function of damage to the hypothalamic-pituitary tract [16]. Clinical distinction between hyponatremia secondary to SIADH and that caused by CSW may be difficult. The critical difference between the two conditions is that CSW involves renal salt loss leading to hyponatremia and volume loss, whereas SIADH results in hyponatremia (typically euvoletic) related to water retention [43].

Hyponatremia is relatively common after general surgery. In a prospective study of 1,088 patients who underwent a variety of surgeries, including cardiovascular, gastrointestinal, renal transplantation, and orthopedic procedures, about 5% demonstrated the disorder. Overzealous administration of hypotonic fluid can contribute to postoperative hyponatremia, which is often attributed to SIADH [44].

Drug-Associated Hyponatremia

A wide range of drugs has been associated with the development of hyponatremia and SIADH [6], including commonly used nonsteroidal anti-inflammatory drugs, acetaminophen, nicotine, the oral antidiabetic agent chlorpropamide, and the antiepileptic drugs carbamazepine and oxcarbazepine [7, 42]. Antineoplastic agents, including vincristine, vinblastine, cyclophosphamide, and ifosfamide, and the antipsychotic medications, thiothixene and haloperidol, can also cause SIADH by increasing AVP release [42]. Angiotensin-converting enzyme inhibitors may also cause SIADH, but the mechanism underlying this effect has not yet been determined [45]. For example, diuretics can stimulate AVP release by inducing hypovolemia. They also impair urinary dilution and alter osmoreceptor sensitivity and thirst by depleting potassium [25]. Thiazide diuretics interfere with urinary dilution at the distal tubule and may be associated with a particularly high risk for the development of hyponatremia. In a review of 129 case reports of hyponatremia, thiazide diuretics were involved in 73% of cases [18].

The tricyclic antidepressant, clofibrate, and the serotonin-selective reuptake inhibitors (SSRIs) can lead to increased AVP release and hyponatremia [42]. In a series of patients taking SSRIs, symptomatic hyponatremia due to SIADH occurred in 12.5% and asymptomatic hyponatremia was noted in an additional 12.5% [45]. In a retrospective case-note study, hyponatremia occurred in 40% of 15 elderly patients with depression within 2 weeks after the initiation of treatment with the SSRI, paroxetine. The secretion of AVP was elevated in these patients despite their having low serum osmolality [46]. A second study by the same group revealed the rapid development of hyponatremia in 12% of a cohort of 75 elderly depressed patients who initiated therapy with paroxetine [47]. Case reports describing the development of hyponatremia in elderly patients who had hypertension and depression suggest that the combination of an SSRI and a thiazide diuretic may act synergistically to impair renal free water clearance (FWC), leading to severe hyponatremia [48].
AVP Dysregulation and Abnormal Water Balance in the Elderly

Elderly individuals are at the highest risk of having hyponatremia, owing to a number of predisposing, age-related physiologic changes [6]. First, an age-related decrease in total body water (relative and absolute) renders elderly persons more susceptible to water imbalance [49, 50]. Second, the thirst mechanism diminishes with age, thereby significantly impairing the ability to maintain homeostasis and increasing the risk of dehydration [49, 51]. Third, the aging kidney contains fewer glomeruli, leading to decreased renal blood flow and a lower glomerular filtration rate. This change in renal function results in increased passive reabsorption of water in the distal tubule and impaired urinary diluting capacity [6]. The increased secretion of AVP and reduced sensitivity of the cyclic adenosine monophosphate response to AVP in the aging kidney can also decrease urinary dilution and FWC [6, 52].

The risks of the dysregulation of water balance and hyponatremia are also increased in older individuals by an age-related rise in AVP secretion per unit increase in plasma osmolality. This change may be caused by the enhanced sensitivity of osmoreceptors or increased osmoreceptor-induced AVP release in older individuals [7].

The risks for hyponatremia in the elderly are also elevated when they take certain drugs (e.g. diuretics, antidepressants) known to be associated with the development of this condition [4, 47].

AVP Dysregulation and Fluid Retention in CHF

Reduced cardiac output in patients with CHF stimulates increased secretion of AVP and the activation of both the RAAS and the sympathetic nervous system [53, 54]. The synthesis and plasma levels of AVP are significantly and chronically elevated in patients with CHF despite the presence of volume overload, atrial distension, hyponatremia, and low plasma osmolality that would normally inhibit AVP release [31, 55]. The non-osmotic release of AVP is apparently caused by disturbances in circulatory homeostasis, such as arterial underfilling [55]. Elevated levels of AVP have adverse effects on hemodynamics and cardiac remodeling and potentiate the vascular and cardiac effects of norepinephrine and angiotensin II [31]. Excessive AVP secretion is a possible contributing factor for increased systolic and diastolic wall stress via $V_{1A}$ and $V_2$-mediated effects on the peripheral vasculature and on water retention [56]. By increased activation of $V_{1A}$ receptors, AVP may have a direct adverse effect on myocardial contractility and cell growth [56, 57]. Indeed, hyponatremia induced by excess AVP has been shown to be an independent risk factor for death in patients with CHF [58].

AVP Dysregulation and Hyponatremia in Cirrhosis

Hyponatremia is frequently seen in patients with cirrhosis. Evidence suggests the hyponatremia of cirrhosis is dilutional and is a result of impaired water excretion. Patients with cirrhosis and ascites usually have a marked decrease in systemic vascular resistance and mean arterial pressure. In an animal study of cirrhosis, these changes were related to increased generation of nitric oxide [59]. Further, a reduction in pressure sensed by baroreceptors leads to activation of neurohormonal mechanisms including RAAS, sympathetic nervous system activation and more importantly AVP release in an attempt to restore perfusion [32, 60]. Another renal mechanism for water retention may be reduced renal prostaglandin synthesis and decreased distal tubule delivery [60]. In the early course of disease, water excretion is usually normal but becomes increasingly impaired as the liver disease progresses and is largely related to the increased release of AVP. The increase in AVP secretion is roughly proportional to the severity of the disease, so the degree of hyponatremia may also correlate with the severity of parenchymal liver disease [32].

AVP Receptor Antagonism

The selective blockade of the appropriate AVP receptors is a rational therapeutic approach in the treatment of dilutional hyponatremia [29, 32, 61, 62]. These agents treat the effects of increased serum levels of AVP more directly than conventional therapies, such as fluid restriction, saline infusions, diuretics, lithium, demeclocycline, and urea (table 1) [25, 63]. The $V_2$ receptor, which is expressed primarily in the kidney, presents an ideal target for modulating the effects of AVP on water balance [32]. During the normal renal escape from water loading and AVP elevation, expression of the $V_2$ receptor and its associated AQP is downregulated [37, 38]. Unlike diuretics, $V_2$ receptor antagonists stimulate free water excretion without Na+ or K+ loss (fig. 1) [64, 65]. Antagonism of the $V_2$ receptor stimulates water excretion without compen-
satory activation of the RAAS, another undesirable effect of loop diuretics [66]. The use of an AVP receptor antagonist to treat hyponatremia has other advantages over existing therapies. In patients with CHF, AVP antagonism has the potential to produce effective and sustained reductions in congestion without worsening renal function, potassium depletion, or hypotension that may be associated with diuretics [67]. In low-output CHF, V₂ receptor antagonists can correct the associated conditions of hyponatremia, hypo-osmolality, and water retention [54]. AVP receptor antagonists that block both V₂ and V₁A receptors may provide additional benefits in patients with hyponatremia caused by edematous conditions, such as CHF, because they have the potential to counteract water retention in the kidney, inhibit ventricular remodeling, lower blood pressure, and decrease the risk of coronary vasospasm [68, 69].

**V₂ Antagonism in Hyponatremia**

Antagonists of V₁A and V₂ receptors are currently under investigation for the treatment of hyponatremia due to CHF, hypertension, cirrhosis, and the nephritic syndrome [32, 61]. These drugs were effective, safe, and well tolerated in early-stage clinical trials [70]. The inhibition of AVP at the V₂ receptor induces aquaresis (fig. 1), the elimination of free water without depleting electrolytes or activating neurohormonal systems [34]. Thus, these antagonists appear to be particularly useful for treating water retention and hyponatremia in SIADH and hepatic cirrhosis [32, 62].

**SIADH**

In a study of 6 patients with SIADH and 5 with cirrhosis [71], treatment twice daily with 50 or 100 mg of the oral V₂ receptor antagonist lixivaptan (VPA-985) increased the serum [Na⁺] from 126 to 133 mEq/l during a 24-hour period in patients with SIADH. This rise was associated with a significant decrease in Na⁺ excretion, from 82 to 45 mEq/l/24 h. Lixivaptan (25, 125, or 250 mg/day) has also been evaluated in a larger sample of 44 patients with hyponatremia. As in the smaller study, lixivaptan produced a significantly greater aquaretic response than the placebo did, with significant dose-related increases in FWC and serum [Na⁺] [72].

**CHF**

The V₂ receptor antagonist tolvaptan has been evaluated in patients with CHF in two large-scale studies. The first study enrolled 254 patients with CHF, 28% whose serum [Na⁺] was <136 mEq/l at baseline. Patients were randomly assigned to 25 days of treatment with placebo or 30, 45, or 60 mg tolvaptan without fluid restriction and while maintaining stable doses of furosemide [73]. In the subgroup of patients with hyponatremia, tolvaptan produced significantly greater increases in serum [Na⁺] than placebo, with the majority of patients achieving normal serum [Na⁺] by day 1 and throughout the end of treatment [73]. In a second randomized, double-blind, placebo-controlled, parallel-group trial, the safety and efficacy of tolvaptan (30, 60, or 90 mg/day for up to 60 days) was evaluated in 319 patients with a left ventricular ejection fraction of <40% who were hospitalized for worsening symptoms of CHF [74]. Sixty-eight patients had hyponatremia (serum [Na⁺] <136 mEq/l) at baseline. Tolvaptan produced a rapid increase in serum [Na⁺] in this subpopulation, and often a normalization that persisted throughout the study [74]. A single dose of OPC-31260 (0.25 or 0.5 mg/kg) increased urine volume and decreased urinary osmolality to <225 mosm/kg in 11 patients with hyponatremia and SIADH [75].

Combination therapy with AVP antagonism and ACE inhibition has been studied in animal models and shown to improve left ventricular function [57]. Investigators demonstrated that combination therapy using conivaptan with or without captopril in a rat model of CHF showed an increase in free-water excretion and also significantly lowered blood pressure, ventricular (left and right) and lung mass. Indeed, simultaneous antagonism of V₁ and V₂ receptors and inhibition of the renin angiotensin system may be effective in managing hyponatremia in CHF.

**Cirrhosis**

In a study of 8 patients with cirrhosis and ascites or peripheral edema, a single 30-mg dose of OPC-31260 significantly increased the urinary excretion rate within 2 h and significantly lowered urine osmolality 2–4 h after administration. FWC was also significantly increased within 4 h after administration [76].

Further, V₂ receptor antagonism has also shown efficacy in correction of dilutional hyponatremia in patients with cirrhosis in a study of 60 patients [60]. Patients were randomized to placebo or 50 or 100 mg lixivaptan (VPA-985) twice a day with concomitant fluid restriction. There was a significant dose-dependent increase in the serum sodium concentration in treated patients by at least 5 mmol/l: 67% in the 200-mg group; 45% in the 100-mg group, and only 15% in the placebo group (p < 0.01). A complete response (serum sodium concentration
Hyponatremia is a common electrolyte disorder that affects as many as 22% of hospitalized patients. It can be caused by any condition that increases the ratio of total body water to serum [Na⁺], and it is often associated with AVP dysregulation, such as in SIADH. The dysregulation of AVP secretion and hyponatremia are particularly common in the elderly and caused by many drugs and certain types of surgery. Conventional treatments for hyponatremia (e.g. fluid restriction, diuretic treatment, and Na⁺ replacement) may not be effective in all patients with hyponatremia and can result in significant adverse events. Preclinical and clinical trial results have shown that aquaresis achieved with AVP receptor antagonism is a rational and highly promising approach to the treatment of hyponatremia that, unlike diuretic therapy, directly addresses the effects of elevated AVP that cause this clinically important electrolyte imbalance. AVP antagonists promote the renal excretion of free water and thereby increase serum [Na⁺], without activating neurohormonal systems.

**Conclusions**

Vasopressin Dysregulation and Hyponatremia

>136 mmol/l) was observed in 50% of patients in the 200-mg group, 27% of patients in the 100-mg group, and none in the placebo group (p < 0.01 and p < 0.05 for 200 and 100 mg VPA compared with placebo group, respectively) [60]. There was no significant difference between groups in the development of renal insufficiency noticed. Indeed, V₂ receptor antagonism may increase the plasma AVP concentration by affecting a negative feedback mechanism which may lead to an unopposed hyperstimulation of the vasoconstrictor V₁ receptors. Theoretical potential hyperstimulation of the vasoconstrictor V₁ receptors may have a beneficial effect in patients with cirrhosis by decreasing pressure in the portal circulation and potentially decreasing risk of variceal bleeding [32].

**V₁A/V₂ Receptor Antagonist**

A V₁A/V₂ receptor antagonist provides V₂-mediated renal aquareasis and may suppress the negative hemodynamic and cardiac effects caused by activation of the V₁A receptor [34, 67]. Conivaptan (YM-087) is currently the only agent in this class [77] and has recently been approved by FDA. In an early pharmacokinetic/pharmacodynamic study of conivaptan in healthy volunteers, the drug was well tolerated, increased urine flow, lowered urine osmolality, and increased plasma osmolality [78].

In several small-scale open-label studies, conivaptan produced significant aquareasis in patients with either CHF or SIADH and hyponatremia. In a study of 6 patients who had hyponatremia and CHF before undergoing heart transplantation, conivaptan (20–120 mg twice daily) increased FWC and serum [Na⁺], changes that persisted for several weeks after the discontinuation of conivaptan [79]. In another open-label study of 6 patients with hyponatremia and CHF awaiting transplant, conivaptan (10–60 mg twice daily) increased the average serum [Na⁺] by 5 mEq/l and maintained it ≥4 mEq/l above baseline for 1 week after the end of treatment. Conivaptan also decreased urine osmolality and increased urine output and FWC [80]. The effects of intravenous conivaptan (up to 40 mg day) were evaluated in 8 patients with hyponatremia (4 patients with SIADH and 4 with CHF). After 3 days of treatment, the patients’ average [Na⁺] increased to 131 mEq/l and their urinary [Na⁺] osmolality decreased from 380 to 292 mosm/kg. Their FWC increased from 364 to 484 ml [81].

In a larger double-blind trial, 142 patients with symptomatic CHF (New York Heart Association class III and IV) were randomly assigned to receive a single intravenous dose of conivaptan (10, 20, or 40 mg) or placebo. The 20- and 40-mg conivaptan doses reduced pulmonary capillary wedge pressure significantly more than placebo. Conivaptan also increased urine output significantly during the first 4 h after administration. In addition, conivaptan had no significant effects on blood pressure or heart rate in patients with advanced CHF [68]. Conivaptan (20–80 mg daily) was administered to 5 patients who had SIADH and a baseline [Na⁺] of <132 mEq/l. In each of these patients, conivaptan normalized [Na⁺], increased FWC, and decreased urine osmolality [82]. Conivaptan has also been evaluated in several recently completed clinical trials of patients with euvoletic or hypervolemic hyponatremia. In a randomized, double-blind, multicenter, placebo-controlled, parallel-group study, intravenous conivaptan (a 20-mg loading dose followed by continuous infusion of 40 or 80 mg/day for 4 days) was compared with placebo in 84 patients. Both conivaptan doses were significantly more effective than placebo in increasing serum [Na⁺] and effective water clearance, a measure of electrolyte-free water excretion [83]. In two similar studies, 83 and 74 patients, respectively, with euvoletic or hypervolemic hyponatremia were given oral conivaptan, 40 or 80 mg/day, or placebo for 5 days. Results indicated that conivaptan improved [Na⁺] and other efficacy measures significantly more than placebo [84, 85].
References

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