

Vasopressin antagonists in treatment of hyponatremia

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Abstract: Hyponatremia is the most frequently encountered electrolyte disturbance in hospitalized patients. It is usually caused by dysregulation of arginine vasopressin (AVP) homeostasis associated with water retention such as congestive heart failure and cirrhosis, or following euvoletic states such as syndrome of inappropriate secretion of antidiuretic hormone. Available therapy, i.e. restriction of fluid intake, saline and diuretics, is often ineffective with unpredictable results and potentially serious side effects. Recent clinical trials with non-peptide AVP receptor antagonists (vaptans) have indicated that these drugs are effective in the treatment of hyponatremia. Vaptans lead to aquaresis, an electrolyte-sparing excretion of free water, that results in the correction of serum sodium concentrations. Until now the Food and Drug Administration in the USA has approved the use of intravenous conivaptan for treatment of euvoletic hyponatremia. In this article, we review results from recent clinical trials on vaptans (lixivaptan, tolvaptan, conivaptan and satavaptan) which showed their efficacy in the treatment of hyponatremia.

Key words: hyponatremia, vaptans, vasopressin, vasopressin antagonists

Hyponatremia is a common electrolyte disorder that frequently develops in hospitalized patients. It can lead to the life-threatening condition. Apart from dehydration, the causes of hyponatremia are disturbances of vasopressin secretion in the course of congestive heart failure (CHF), liver cirrhosis, renal diseases and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Until now, the available therapeutic options for the treatment of these diseases are of limited efficacy. Studies on a new class of drugs showed efficacy and safety in the treatment of hyponatremia associated with CHF, liver cirrhosis or SIADH. This class represents vasopressin receptor antagonists - nonpeptide receptor antagonists (vaptans). The V_2 antagonists, called also aquaretics, act directly on vasopressin receptors, which are located in the distal nephron, leading to aquaresis, diuresis with an increase free water loss. It has been reported that the use of these agents increases serum sodium levels, reducing urinary sodium concentrations and urine osmolality.

Hyponatremia

Hyponatremia, being the most common electrolyte disturbance, occurs in 3–15% of hospitalized patients [1–3]. Hyponatremia is defined as a decrease in the serum sodium level below 135 mmol/l. Advanced age is a risk factor for hyponatremia. In patients between 51 and 60 years, this risk is two times higher than in 30-year-old patients, and even 5 times higher in patients aged >70 years [4].

The clinical manifestations of hyponatremia depend on the time of its duration, velocity of the sodium level decrease, patient age and serum Na levels [5–7]. If hyponatremia lasts for 48 hours, it is acute. If the duration of this disorder is longer than 48 hours, hyponatremia is chronic [7]. Symptoms are more severe in acute hyponatremia because the brain cannot adapt rapidly to the change in serum sodium [6]. More symptoms result from cerebral edema and encephalopathy [8,9]. The cerebral edema results from a shift of water from hypotonic extracellular fluid to the intracellular space [1]. Patients with chronic hyponatremia may be asymptomatic or have few symptoms. Clinical symptoms are less severe compared to acute hyponatremia (low Na levels in ECF for about 48 hours) because the brain can compensate the fall in serum sodium through the excretion of organic and non-organic solutes.

Most patients with a serum sodium level from 125 to 134 mmol/l are asymptomatic or complain of fatigue. Further decrease in sodium levels results in nausea, vomiting, anorexia,

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malaise, and behavioral alterations. Reduction below 120 mmol/l causes the appearance of convulsions, disturbed consciousness, and finally coma [2,7].

Based on medical history and the physical examination, hyponatremia can be classified into hypovolemic, normovolemic and hypervolemic. This division is of importance given different pathologic mechanisms leading to the development of hyponatremia and different management methods of hyponatremia.

Hypovolemic hyponatremia is the consequence of vomiting, diarrhea, use of diuretics and excessive sweating. If a patient supplements fluid loss by drinking hypotonic beverages, hyponatremia is more pronounced. Antidiuretic hormone secretion is increased as part of the compensatory response to defend against volume contraction, which however only enhances water reabsorption [1-3].

The SIADH (Schwartz and Bartter syndrome) is the most common cause of normovolemic hyponatremia. This disorder may be caused by hypophyseal adenoma, lung cancer, pancreatic carcinoma, thymoma secreting ectopic hormones. The hypersecretion of antidiuretic hormone (ADH) was also observed in patients with porphyria, pulmonary inflammatory states and encephalitis. A number of drugs, in pathological conditions, can induce antidiuretic hormone secretion; among them the most commonly mentioned in context of the SIADH are chlorpropamide, carbamazepine, amitriptyline, tiordazine and cyclophosphamide.

Levels of SIADH can be markedly elevated compared with those encountered in healthy individuals or be close to the upper limit of the reference range that are too high with regard to effective molality of the body fluid. Patients with SAIDH usually do not demonstrate any clinical signs of overhydration. The main features of SAIDH include hyponatremia, the absence of clinical evidence of volume depletion, continued renal excretion of sodium, inappropriate urine osmolality, normal renal and adrenal function. There are usually low levels of serum creatinine and uric acid. Hyponatremia associated with euvolemia is also observed in hypothyroidism and adrenocortical insufficiency as a result of increased sensitivity of renal tubules to ADH [3,12].

Hypervolemic hyponatremia is frequently encountered in hospitalized patients. Heart failure (HF), liver cirrhosis, acute and chronic renal failure and nephritic syndrome can be the causes of this type of hyponatremia [1,12]. Despite overhydration observed in these disorders, the effective volemia is diminished. Inadequate renal perfusion and that of baroreceptors in the carotid sinuses and aortic arch stimulate excessively the RAA and vasopressin release. Negative nitrogen balance, in this case, may be due to secondary hyperaldosteronism and excessive amount of ADH [1,3,13]. In renal and liver insufficiency, hyperaldosteronism is caused by increased synthesis and also impaired elimination of aldosterone.

Conventional treatment for euvolemic and hypervolemic hyponatremia

Currently available conventional therapies are of little efficacy and are hard to accept for the patient. They may also aggravate the underlying disease. The choice of the therapeutic method is determined by the cause, clinical signs and symptoms, concomitant diseases and rapidity of decrease in sodium levels [12]. for hyponatremia include water restriction, hypertonic saline, furosemide, demeclocycline, urea and lithium [1,2,10-14]. Demeclocycline and lithium are used very rare. Due to significant side effects, lithium actually is not used [1,2].

Patients who have acute, symptomatic hyponatremia should receive the infusion of hypertonic saline, with a rate of increase in sodium levels not exceeding 1–2 mmol/l per 1 hour. The goal is to raise sodium serum level by no more than 8–12 mmol/l within the first 24 hours. Simultaneously, the treatment involves also water restriction [1,2,10-14].

In case of chronic hyponatremia sodium levels should be corrected more slowly, not faster than 0.5 mmol/l/h, with recommendation of restricted fluid volumes consumed below 750–1250 ml/d. Moreover, isotonic saline solutions are preferable to hypertonic ones. The latter is reserved to patients with severe neurological signs and symptoms. Within 24 hours natremia may increase not more than 8 mmol/l at maximum [14]. If hyponatremia is associated with normal volemia, demeclocycline may be added to the treatment strategy. In hypervolemic patients following initial clinical improvement the treatment might be supplemented by a loop diuretic. Since therapeutic effect is difficult to predict, frequent determinations of serum sodium levels are recommended [1,2,10-14]. Supportive therapy in hypervolemia is to induce osmotic diuresis, most commonly by using 20% mannitol; 100 ml of such a solution is given in a quick intravenous infusion. If diuresis is increased, additional infusion of mannitol can be administered to a total dose of 500 ml. However, this approach is often less effective.

Overly rapid correction of hyponatremia can lead to severe neurological complications. Pontine myelinolysis is the main neurological problem, which occurs a few or more than 10 days after hyponatremia correction [2,11-14]. It is the consequence of damage of oligodendrocytes in the pons and is irreversible [1,2,7]. The most important symptoms of myelinolysis include confusion, behavioral changes, pseudobulbar palsy, dysphagia, dysarthria, seizures, hemiparesis or quadriparesis [7].

Vasopressin antagonists – introduction

All available therapeutic approaches to euvolemic and hypervolemic hyponatremia produce variable and often disappointing results.

First of all, the current therapy does not involve the underlying etiology. Because hyponatremia associated with water retention is a result of excess vasopressin, the most rational approach to therapy for this disorder is to either decrease

the secretion of vasopressin or block its effects on the kidney [3,12,14]. The direct approach involves antagonizing the V_2 receptor. The V_2 receptors can be found on the cells of the collecting duct. The stimulation of V_2 activates adenylyl cyclase and promotes cyclic adenosine monophosphate cAMP and protein kinase A and promotes synthesis aquaporin-2 (AQ2). AQ2 are incorporated into the apical plasma membrane, allowing water to be reabsorbed [3,12,14].

The arginine vasopressin (AVP) receptor antagonists promote aquaresis – the electrolyte – sparing excretion of water. It seems that inhibition of V_2 receptors may be effective treatment for hyponatremia [3,12,14].

The V_{1A} receptors are expressed in vascular smooth muscle cells, cardiomyocytes, platelets and hepatocytes. Their activation can lead to vasoconstriction, increased peripheral vascular resistance, platelet aggregation, inotropic action – positive or negative (independent of the AVP concentration) and cardiomyocyte hypertrophy [3,12,14].

AVP receptor antagonists in the treatment of hyponatremia

Initial development efforts on vasopressin receptor antagonists focused on peptide analogs, derived from the selective V_2 receptor [15,16]. These compounds were useful in evaluating the receptor subtype specificity and binding affinity, and appeared to demonstrate some short-term therapeutic value in the animal models studied. The peptide antagonists had poor oral bioavailability, limiting their utility to parenteral administration [16].

In 1991 Yamamura reported [17] the first use of OPC-21268, V_1 receptor antagonist. Also, the efficacy of OPC-31260, a selective nonpeptide V_2 receptor was described for the first time. Administration of V_2 receptor antagonist has demonstrated to stimulate free water excretion with little to no sodium loss [18]. Accordingly, specific V_2 blockade has been shown to be beneficial in the treatment of SIADH and cirrhosis [18].

Tolvaptan (OPC-41061) was synthesized through a series of structural conversions to the OPC-31260 molecule.

The diuretic response observed with 1–10 mg of OPC-41061 were equipotent to furosemide at doses of 10–100 mg.

When used as a supplement to furosemide therapy, tolvaptan has demonstrated an additive diuretic effect [21].

The role of tolvaptan in patients with hyponatremia has been evaluated in two studies [22,23]. The first study included 28 patients with hyponatremia less than 135 mmol/l [22]. The patients were randomly assigned to receive tolvaptan ($n = 17$), water restriction with placebo ($n = 11$). The patients received tolvaptan at a dose of 10–60 mg per day. The treatment lasted 27 days.

Tolvaptan produced greater increases in sodium levels with 5.7 ± 3.2 mmol/l than did water restriction with placebo with 1.0 ± 4.7 mmol/l.

The Study of Ascending Levels of Tolvaptan in Hyponatremia was randomized and placebo-controlled [23]. The study

included 243 patients with hyponatremia, who received tolvaptan with increased doses of 15–60 mg per day for 30 days. The control group received placebo. Tolvaptan was significantly superior to placebo. There was no response for the treatment with tolvaptan (increase in sodium levels <5 mmol/l) in 37% of patients with cirrhosis, in 17% of patients with heart failure and in 17% of patients with SIADH.

Tolvaptan has also been evaluated in clinical trials with patients with heart failure [23–26]. Hyponatremia was observed in 28% of patients among 254 NYHA class II–III heart failure patients [25,26]. Tolvaptan was administered orally at doses of 30, 45 or 60 mg daily in addition to standard therapy of heart failure.

Reductions in symptoms (ankle edema, lung congestion, increased body weight) were observed irrespective of serum sodium levels at baseline. The aquaresis effect was dose-dependent of tolvaptan. Increase in natremia (in patients with hyponatremia prior to the study) was statistical significant and persisted for more than 25 days after discontinuation of therapy. In the studied population, the serum sodium level increased by no more than 4 mmol/l per day; this increase was not very quick. Hypernatremia developed in 6, 11, 13% of patients treated with tolvaptan at doses of 30, 45, 60 mg per day, respectively, and in 5% among the placebo group. In another study, the role of tolvaptan in normalization of serum sodium without disturbance of electrolytes, especially potassium, apart from subsided clinical signs and symptoms of heart failure, was confirmed [27]. Renal function was not changed [24–27]. The Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure trial was a multi-center, randomized, double-blind trial with 319 patients suffering from acute exacerbation of heart failure [28]. After 24 hours, tolvaptan increased urinary output with reduced osmolality and significantly increased natremia.

In post-hoc analysis, mortality was significantly lower in tolvaptan-treated patients with severe condition at baseline. The most common side effects include thirst and dry mouth.

In March 2007, the results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial with patients suffering from heart failure was published [29]. A multi-center, randomized, double-blind trial was performed in a group of 4133 patients. In the tolvaptan group, after 7 days of therapy, tolvaptan reduced clinical signs and symptoms of decompensated heart failure compared with patients receiving conventional therapy. Renal function was not changed over one year. Mortality and recurrent hospitalizations were also not different compared with standard therapy. This is the first such a large trial with vaptans, and the follow-up is not so long (1 year).

Lixivaptan (VPA-985) is a selective V_2 antagonist receptor. The drug is orally active.

The role of lixivaptan in 60 patients with hyponatremia in the course of cirrhosis has been evaluated in the multi-center, randomized, double-blind trial described by Gerbes et al. [30]. The patients were fluid restricted (<1 l per day). The serum

sodium levels were 115–132 mmol/l at baseline. The doses of lixivaptan were 100 or 200 mg daily. After 7 days of therapy, 27% of patients given lixivaptan 100 mg daily and 50 % patients given lixivaptan 200 mg daily demonstrated normalization of serum sodium, whereas placebo did not. The eunatremia effect was observed mean after 4.8 days for the dose 200 mg or after 5.7 days for 100 mg. The serum sodium level increased 0.8 ± 0.4 mmol per day for 100 mg and 1.8 ± 0.5 mmol per day for 200 mg, maximum was 7 mmol per day. During therapy, lixivaptan produced aquaresis and dose-dependent increase in the free water clearance. Renal parameters did not change; only in patients who received 200 mg lixivaptan, slightly decrease in glomerular filtration was observed. The vasopressin level increased from the baseline 2.05 ± 0.2 pg/ml to 5.7 ± 0.3 pg/ml at the end of the treatment, there were not significant clinical complications associated with this (angina pectoris, bleeding). The most common side effect of lixivaptan was thirst [30].

In another multi-center, randomized, double-blind trial, patients who suffered from heart failure, cirrhosis and SIADH with hyponatremia were treated with lixivaptan [31]. The study included 44 patients, who were assigned to receive placebo or lixivaptan 25, 125 or 250 mg twice a day for 7 days. The patients received also standard therapy (including diuretics) and were fluid restricted (<1.5 l daily). Lixivaptan therapy produced a statistically significant increase in natremia, serum osmolality and aquaresis. The volume urinary excretion and free water clearance increased in accordance with the dosage given. Urinary sodium excretion did not increase with lixivaptan therapy. Glomerular filtration and orthostatic blood pressure did not decrease during therapy. The role of lixivaptan was confirmed only at higher doses (125, 250 mg). Therapy with lixivaptan 250 mg twice a day was associated with a higher prevalence of dehydration, in the results, the patients should be more accurately observed. The main complaint of the patients was thirst. Neurologic side effects were not observed during therapy.

In the second phase trial, the patients with hyponatremia in the course of SIADH or cirrhosis received lixivaptan 50 or 100 mg daily [32]. In the patients with SIADH, over 48 hours, increase in serum sodium levels from 126 ± 5 mmol/l to 133 ± 5.6 mmol/l and decrease in urinary sodium excretion from 82 ± 22 to 45 ± 21 mmol per day were observed. Similar natremia increase was noticed in the patients with cirrhosis after 72 days of therapy (from 126 ± 2.9 to 133 ± 4.9 mmol per day) and slightly increase in urinary sodium excretion – from 23 ± 18 to 65 ± 60 mmol per day was also observed. It seems that this increase in sodium excretion after 72 days of therapy reflected eunatremia. Due to different pathologic mechanisms of hyponatremia in both cases, the different changes in the magnitude of sodium excretion were observed. During therapy of two diseases there was no increase in the rennin-angiotensin-aldosterone activity.

Conivaptan (YM-087), is a vasopressin receptor antagonist, is the first agent in this class to be approved for the treatment of hyponatremia in patients (Vaprisol) [12,33]. Food

and Drug Administration (FDA) approved this drug in 2005. Conivaptan is administered intravenously. Conivaptan is a V_{1A} and V_2 receptor antagonist (10:1) [23,33]. Lack of receptor selectivity is particularly useful in the treatment of heart failure. Additional blockage of V_{1A} receptors results in reduced vascular peripheral resistance and inhibits unfavorable myocardial remodeling. Maximal aquaresis effect of this drug is observed as early as after 2 hours and it is markedly stronger than that of furosemide [24]. The half-time of conivaptan is approximately 5.6 hours [11].

There are now available two trials regarding the use of conivaptan in patients with hyponatremia. In a randomized, double-blind, multicenter, placebo-controlled trial included 74 patients with euvolemic or hypervolemic hyponatremia, who were treated with oral conivaptan [34]. The patients received conivaptan in two doses – 40 or 80 mg per day. In the 40 mg group, the mean increase in sodium levels was 6.4 mmol/l. Serum sodium level increased by 8.2 mmol/l in the higher dose group; there were statistical significant differences compared with the placebo group (increase by 3.2 mmol/l). Normonatremia was achieved in 71% of patients from the 40 mg group, in 82% in the 80 mg group and in 48% in the placebo group (in both groups – in placebo and in conivaptan- standard therapy was maintained). The prevalence of side effects was similar in the conivaptan group and the placebo group. Although effective, the oral preparation is no longer being developed for clinical use because of concerns during the long-term use about interactions with other drugs metabolized by the CYP3A4 pathway. The FDA approved to use conivaptan in intravenous infusion for a short time (maximum 4 days).

In another randomized, multicentre, double-blind trial, the role of conivaptan in 84 patients with normovolemic or hypervolemic hyponatremia secondary to SIADH or to heart failure was evaluated [35]. The serum sodium level at baseline was 115–130 mmol/l. The patients received a 20 mg bolus of conivaptan for 30 min followed by continuous intravenous infusion of 40 or 80 mg conivaptan per day for four days.

A median time to a 4 mmol/l increase in sodium was 23.7 h in the 40 mg group and 23.4 h in the 80 mg group. Conivaptan produces more rapid correction of sodium than selective receptor V_2 antagonists [36]. It can result from enhanced bioavailability of the intravenous preparation. Sodium serum increased by 6 mmol/l or more in 69% of patients who received smaller dose of conivaptan and in 88.5% in the 80 mg – group. During the study, there was no hyponatremia, which can cause neurological consequences. Aquaresis effect was similar for both doses of conivaptan, after 24 hours of therapy, there was increase in diuresis by 1.6 l and 1.75 l per day, respectively.

Conivaptan is indicated for the treatment of euvolemic hyponatremia and hypovolemic hyponatremia in hospitalized patients [33]. The route of administration of this drug is only intravenous. Conivaptan should be given in the 20 mg bolus for 30 min followed by continuous intravenous infusion of 20 mg. Maximum dose is 40 mg per day. The most common

Table. Characteristics of vasopressin receptor antagonists

	Lixivaptan (VPA-985)	Tolvaptan (OPC-41061)	Conivaptan (YM-087)	Satavaptan (SR-121463)
Effect on receptors $V_2:V_{1A}$	100:1	29:1	1:10	112:1
Route of administration	oral	oral	oral	oral
Dosage	twice a day	once a day	continuous infusion	once a day
Na ⁺ excretion/24 hr	↔ small dose ↑ bigger dose	↔	↔	↔
Aquaresis effects	+	+	+	+
Administration	CHF, SIADH, cirrhosis	CHF, SIADH, cirrhosis	SIADH, CHF	SIADH

↔ – unchanged, ↑ – increased, * – acceptable to the treatment
CHF – congestive heart failure, SIADH – syndrome of inappropriate antidiuretic hormone secretion

adverse effect is local reaction at the infusion site, namely pain and local irritation (in 21–52.5% of patients). In 2007, the FDA approved Conivaptan for the treatment of hypervolemic hyponatremia secondary to chronic heart failure. It suggests that this drug may be not used in patients with cirrhosis due to increased risk of variceal bleeding and prevalence of hypotonia [37]. There are evidence that Conivaptan can be added to standard therapy of exacerbation of heart failure, even without accompanying hyponatremia [22,37].

A dose Evaluation of a Vasopressin Antagonist in CHF Patients undergoing Exercise is a trial, in which recently the role of Conivaptan in patients with heart failure is evaluated [38].

Satavaptan (SR-121463) is a V_2 receptor antagonist that have prolonged half-life, which makes it possible to use it once daily. This agent is available as an oral preparation. It has enhanced affinity to V_2 receptors compared to V_{1A} (112:1) [39]. Aquaresis effect appears as early as two hours following the drug administration and persists up to 12 hours [16].

In the phase II trial with 34 patients with SIADH, the efficacy of Satavaptan was evaluated. In the first randomized, double-blind and placebo-controlled part, the patients received Satavaptan at doses of 25–50 mg for 5–23 days [40]. The sodium level was 119–131 mmol/l at baseline. An increase in sodium levels by 5 mmol/l or more or its normalization was observed in 13% of the placebo group, in 79% and 83% of patients who received 25 and 50 mg, respectively. Natremia were 130 ± 5 mmol/l in placebo group, 136 ± 6 mmol/l and 140 ± 6 mmol/l in patients who received Satavaptan at dose 25 and 50 mg respectively, on the fifth day of therapy. Increase in the urine flow rate and decrease in its osmolality by about 50% were observed. In long-term, open label study, the role of Satavaptan was evaluated. The drug was administrated for 12 months and maintained normonatremia effect. The adverse effects were not noticed during the study. As positive effects were observed, Satavaptan entered a phase III trial for the investigation of its efficacy in patients with SIADH [41].

In two multicentre, randomized trials, recently, the efficacy of Satavaptan in patients with cirrhosis is evaluated. One of them is the Cirrhotic Ascites Treatment With Satavaptan in Patients With Ascites Due to Cirrhosis of the Liver, which

evaluates the efficacy of Satavaptan compared with standard therapy in patients with cirrhosis and ascites. In Satavaptan for the Prevention of Ascites Recurrence in Patients With Ascites Due to Cirrhosis of the Liver 1 and 2, the effect of Satavaptan with furosemid or without in prevention of ascites recurrence in patients with cirrhosis is evaluated.

Vaptans can potentially be used to treat and inhibit progression polycystic kidney disease – autosomal dominant (ADPKD).

In January 2007, the Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and Its Outcomes trial has been launched. It evaluates the efficacy of tolvaptan in the inhibition of progression ADPKD.

Vaptans might also be used to treat nephrogenic diabetes insipidus [44].

CONCLUSIONS

Hyponatremia, a serious electrolyte disorder, occurs more frequently in hospitalized patients and is associated with higher risk for mortality. Excessive amount of vasopressin plays a main role in its pathogenesis, which is also independent risk factor for mortality confirmed by study of The Survival and Ventricular Enlargement Trial and studies of Left Ventricular Dysfunction [45].

Until now, the available therapeutic options for treating the euvoletic and hypervolemic hyponatremia have been limited.

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