Arginine vasopressin (AVP) and treatment with arginine vasopressin receptor antagonists (vaptans) in congestive heart failure, liver cirrhosis and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Natig Gassanov, Nasser Semmo, Mariam Semmo, Amir M. Nia, Uwe Fuhr, Fikret Er

Arginine Vasopressin (AVP) and Treatment with Arginine Vasopressin Receptor Antagonists (VAPTANS) in Congestive Heart Failure, Liver Cirrhosis and Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Natig Gassanov[1], Nasser Semmo[2], Mariam Semmo[3], Amir M. Nia[1], Uwe Fuhr[4], Fikret Er[1]

[1] Department of Internal Medicine III, University of Cologne, Germany

[2]Department of Medicine II, University Hospital Freiburg, Freiburg, Germany

[3]Department of Nephrology, University Hospital Freiburg, Freiburg, Germany

[4] Department of Pharmacology, University of Cologne, Germany

Keywords: vasopressin, vaptans, hyponatremia, heart failure, SIADH

Correspondence:

Priv-Doz. Dr. F. Er (fikret.er@uk-koeln.de)

Department of Internal Medicine III, University of Cologne

Kerpener Str. 62, 50937 Cologne, Germany

Phone: +49-221-47832544

Fax: +49-221-478 32712

Abstract

Arginine vasopressin (AVP) is the major physiological regulator of renal water excretion and blood volume. The AVP pathways of V_{1a}R-mediated vasoconstriction and V_2R-induced water retention represent a potentially attractive target for therapy of edematous diseases. Experimental and clinical evidence suggests beneficial effects of AVP receptor antagonists by increasing free water excretion and serum sodium levels. This review provides an update on the therapeutic implication of newly developed AVP receptor antagonists in respective disorders such as chronic heart failure, liver cirrhosis and syndrome of inappropriate antidiuretic hormone secretion.

Introduction

Arginine vasopressin (AVP), also known as antidiuretic hormone, is the major physiological regulator of renal water excretion and blood volume. AVP is synthesized in the neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and stored in neurosecretory granules in the posterior pituitary gland. Although increased plasma osmolality is the major regulator of AVP release [1, 2], AVP can be released upon both, osmotic and non-osmotic stimulation **(Figure 1)**. Osmoreceptors with an extraordinary high sensitivity to changes in plasma osmolality reside in the hypothalamus. Thus, an increase of only 1% in plasma osmolality induces AVP release into the circulatory system [2]. The osmotic threshold for AVP secretion is approximately 280 mmol/kg [3] and can be modified under certain circumstances, e.g. changes in blood pressure or in circulatory blood volume, or by pregnancy. A decrease of 5-7% in mean arterial pressure or reduction of 8-10% in plasma volume are generally sufficient to trigger detectable increases in AVP serum levels [4]. An increase in AVP secretion leads to thirst with consecutive increased water intake and antidiuresis, both resulting in an increased arterial circulating volume and decreased plasma osmolality.

AVP actions are mediated by at least 3 different G-protein-coupled receptors called V_{1a}, V_{1b} (also known as V_3) and V_2 **(Figure 2)**. The V_{1a} receptor ($V_{1a}R$), abundantly expressed in vascular smooth muscle cells, hepatocytes and platelets, and the V_{1b} receptor ($V_{1b}R$), predominantly found in the anterior pituitary gland, are linked to the phosphoinositol signalling pathway with intracellular calcium as second messenger. In contrast, the V_2 receptor (V_2R) is coupled to adenylate cyclase signalling with intracellular cAMP as the second messenger. V_2R has long been thought to be exclusively expressed in renal tubules [5], but there is increasing evidence of extrarenal V_2R expression [6-8]. $V_{1a}R$ mediates vasoconstrictive effects, while V_2R regulates water re-absorption in the renal collecting ducts. Stimulation of this receptor induces an intracellullar cascade that promotes trafficking of

preformed aquaporin 2 (AQP2) water channels from the cytosol to the apical plasma membrane [9]. The physiologic role of the V_3R is not completely understood, it is presumed to be involved in corticotropin and glucagon release [10, 11] in addition to cellular proliferation and differentiation effects [12].

Dysregulation of this meticulously controlled feedback system in edematous diseases is mainly caused by sustained or even increased AVP secretion despite of hypoosmolality. A low effective circulating blood volume like in chronic heart failure (CHF), advanced liver cirrhosis or volume depletion activates baroreceptors in the carotid sinus, aortic arch and in the left atrium. Their stimulus for AVP secretion overrides osmotic signals and results in hyponatremia as a part of compensatory responses [13]. Persistent AVP secretion may also occur in tumor cells, which is one cause of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). A wide range of substances involving a neurohormonal antagonism has been developed aiming to alleviate congestion and to improve hemodynamics both acutely and chronically. This review discusses therapeutic implications of newly developed AVP receptor antagonists in CHF, liver cirrhosis and SIADH based on the latest available clinical data.

Pathogenesis of water retention in heart failure

The pathophysiology of CHF is complex and involves interplay of multiple neurohumoral and cellular systems. Decrease in left ventricular (LV) systolic and diastolic function results in reduced cardiac output, stroke volume and intraarterial blood volume. Arterial underfilling, sensed by arterial baroreceptors in the aortic arch and intrarenal sensors, leads to the subsequent activation of the sympathoadrenal system and release of a cascade of neurohormones aimed at correcting the arterial hypovolaemia and restoration of organ perfusion.

Early compensatory mechanisms include vasoconstrictive and sodium retentive actions mediated by the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system, AVP, thromboxane and endothelin [14-16]. These sodium- and volume retaining mechanisms are counter-balanced by the enhancement of the vasodilatory, natriuretic hormonal or cytokine systems, including the natriuretic peptides, prostaglandins, bradykinin and nitric oxide [17, 18].

Initially, these important compensatory mechanisms act to maintain blood pressure and adequate tissue perfusion [19]. However, prolonged activation of these systems, e.g. in patients with CHF, leads to a vicious cycle of hemodynamic alterations, which ultimately deleteriously affects cardiac and renal function.

Currently, diuretics are the widely used therapy in CHF to reduce fluid overload. While rapid symptomatic improvement and a decrease in volume overload are observed with diuretic therapy especially for acute decompensated CHF (ADHF), therapy with diuretics is associated with several adverse effects, such as increased neurohormonal activation, worsening renal function, and electrolyte disturbances [20, 21].

Although patients with CHF are hypervolemic with lower plasma osmolality and serum sodium levels, AVP serum levels are elevated in CHF due to the lower effective arterial blood volume, decreased cardiac output and angiotensin II-induced AVP release. Indeed, AVP serum level is a prognostic parameter and correlates with the severity of cardiac impairment [22, 23]. AVP exerts adverse effects in CHF by increasing peripheral resistance via $V_{1a}R$ - mediated vasoconstriction and by enhancing water retention through effects at the renal V_2R [24, 25]. Furthermore, sustained stimulation of $V_{1a}R$ in the heart can lead to remodelling by stimulating cell hypertrophy [26] and further deteriorates cardiac function **(Figure 3)**. Therefore, blockade of the AVP system may prove as a useful adjunct or alternative to standard therapy in CHF.

Pathogenesis of water retention in liver cirrhosis

Like the compensatory mechanisms in CHF, activation of neurohumoral systems in liver cirrhosis aims to preserve circulatory homeostasis and to maintain arterial pressure. Impairment of water excretion is a common feature of patients with liver cirrhosis. Up to 75% of patients with cirrhosis have an impaired free water clearance after a water load [27]. In the early stage liver cirrhosis is characterized by peripheral vasodilatation and splanchnic venous pooling, which in turn will result in a decreased vascular resistance. The arterial underfilling leads to a non-osmotic baroreceptor-triggered AVP release and water retention followed by dilutional hyponatremia [28]. Secondary to the arterial vasodilatation the sympathetic system is activated. Arterial underfilling is a strong stimulus for the sympathetic nervous system. Via β-adrenergic stimulation, it in turn results in activation of the renin-angiotensin-aldosterone system (RAAS) and renal sodium retention. Angiotensin activates receptors in the proximal tubule epithelium, enhancing sodium reabsorption and impairment of the normal feedback mechanism via aldosterone in the distal nephron.

Bichet et al. studied the AVP response in cirrhotic patients upon a standard water load[29]. There was a significant difference in the AVP response between patients excreting more than 80% of their water load within 5 hours in comparison to patients impaired to excrete the water load who were unable to suppress AVP secretion adequately. Furthermore, significantly higher levels of norepinephrine, renin activity and aldosterone in nonsecreting patients were shown, indicating that increased sympathetic activity, as assessed by plasma levels of norepinephrine, correlates closely with sodium and water retention in cirrhotic patients and thus may be of pathogenetic importance [30]. There is growing evidence linking adverse outcome to increased AVP levels in liver cirrhosis, reflecting the severity of disease [28]. Plasma sodium concentrations of less than 130 meq/L in cirrhosis are associated with a median transplant-free survival of less than 6 months [31]. In addition hyponatremia can cause neurological disturbances which contribute to the overall morbidity of these patients.

Therapy of water retention in liver cirrhosis consists in water and sodium restriction as well as in the application of loop diuretics to induce natriuresis and spironolactone to overcome the effects of hyperaldosteronism. New strategies in the therapy of water retention and hyponatremia in liver cirrhosis include vaptans and the possibility of combining diuretics with new drugs in order to achieve a better control of ascites, without increasing the risk of side-effects.

Pathogenesis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hyponatremia is frequently found in hospitalized patients. Clinical assessment of volume status in addition to urine and blood osmolality analysis often allows differentiation between hypervolemic and euvolemic hyponatremia **(Figure 4)**.

Hyponatremia due to SIADH is common and the causes for SIADH are manifold [32]. The SIADH consists of the following features: hypotonic hypoosmolality with an osmolality < 275 mosm/l, inappropriate high urine osmolality > 100 mosm/l, increased natriuresis< 40 mmol/l and euvolemia. Binding of AVP to the V2-receptor at the collecting duct leads to phosphorylation of AQP-2. Phosphorylated AQP-2 is then inserted in the apical plasma membrane and contributes to the re-absorbtion of free water. Despite hypotonicity patients with SIADH continue to drink because the negative feedback loop is too weak to suppress thirst in these patients [33]. In summary total body water increases and dilutional hyponatremia develops. A common cause of SIADH (80% of patients) is ectopic hormone production by cancer such as oat cell carcinoma of the lung [34]. It has been reported that 19.5% of patients with study-defined hyponatremia died during hospitalization, compared with 6.3% of the entire cancer population [32].

Other causes of SIADH are neurological surgery, trauma, pulmonary, endocrine, and neurologic diseases. Also, a wide range of drugs including antiinflammatory drugs, tricyclic antidepressants, serotonin-selective reuptake inhibitors and some antineoplastic agents, may

cause of SIADH [35-37]. In contrast to hyponatremia in CHF or liver cirrhosis, hyponatremia in SIADH is typically associated with higher urine sodium concentration **(Figure 4).**

Taken together, the hyponatremia in CHF, liver cirrhosis and SIADH is thought to stem from a decrease in effective arterial volume, which triggers baroreceptor activation, increases sympathetic activity, aldosterone secretion, sodium retention and AVP release, resulting in water retention and dilution of total body sodium.

Vasopressin receptor antagonists

The first AVP peptide antagonists were described in the 1970s by Mannig and Sawyer [38]. Despite their antagonistic effects in animals, their use in the therapy of edematous disease was hampered by marked species-differences, partial agonist actions, poor bioavailability and a short half-life. As a result of the subsequent developmental research, the first non-peptide V_2R antagonist was characterized by Yamamura in 1992 [39]. The non-peptide antagonists are orally active and appear to be more bioavailable with longer half-lives than the earlier peptide substances. Several non-peptide AVP receptor antagonists, also known as "vaptans", have been developed and studied in human clinical trials. These vaptans include the dual V_{1a}/V_2R antagonist conivaptan and the specific V_2R antagonists tolvaptan, lixivaptan and satavaptan. The pharmacological properties and chemical structures of these compounds are outlined in **Table 1** and in **Figure 5**.

Some of these drugs are now in clinical use, mainly for the treatment of euvolemic or hypervolemic hyponatremia and for water retentive states such as cirrhosis or CHF. In this review we will summarize available clinical data on most extensively studied vaptans (tolvaptan, conivaptan, lixivaptan and satavaptan) with their potential application in CHF, liver cirrhosis and SIADH **(Table 2)**.

V_2R antagonists

Tolvaptan

Tolvaptan is an oral, selective non-peptide vasopressin V_2R antagonist without intrinsic agonist properties. In *in vitro* studies, tolvaptan blocked the binding of AVP to cloned human V_2R and $V_{1a}R$ with an inhibition constant (K_i) of 0.43 and 12.3 nM, respectively, showing higher V_2R- selectivity [40].

The usual dosage for the approved indications is 15 mg daily and should be initiated in hospital; the maximum dosage should not exceed 60 mg once daily. Generally, no dosage adjustments are necessary in patients with hepatic or renal (creatinine clearance rate ≥10 ml/min) impairments. Tolvaptan should not be used in hypovolemic hyponatremia and is contraindicated in anuric patients.

Tolvaptan has linear pharmacokinetics and is primarily metabolized by CYP3A4 [41]. Though the results of clinical studies showed that tolvaptan was safe and well tolerated in humans, tolvaptan has the potential for a number of clinically relevant drug interactions, particularly with CYP3A inhibitors. Less than 1% of the substance is eliminated unchanged via the urine [42]. In human, increases in tolvaptan concentrations (C_{max}) were less than dose-proportional and plateaued at doses greater than 240 mg [43]. The most frequent adverse events reported in clinical trials were thirst, frequent urination and dry mouth [44].

CHF. Tolvaptan has extensively been characterized in patients with CHF. In a double-blind, placebo-controlled study on 254 patients with New York Heart Association (NYHA) class II or III CHF, tolvaptan added to standard therapy including non-potassium-sparing diuretics resulted in a significant decrease in body weight in the 30, 45 and 60 mg tolvaptan groups (-0.79 ± 0.99, -0.96 ± 0.93, and -0.84 ± 0.02 kg; $p<0.001$ for all treatment groups versus placebo), normalization of serum sodium and increase in urine volume (3.9 ± 0.6, 4.2 ± 0.9, 4.6 ± 0.4, and 2.3 ± 0.2 l/24 hours; $p<0.001$) at day 1 without causing hypokalemia or worsening renal function [45].

The short- and intermediate-term effects of tolvaptan were further examined in the ACTIV in CHF trial [46]. In this trial, 319 patients hospitalized with CHF were randomized to 30, 60, 90 mg/d tolvaptan or placebo for up to 60 days in addition to the standard therapy. The primary inpatient outcome was change in body weight at 24 hours after the administration of the first dose of study drug. The primary outpatient end point was worsening CHF at 60 days after randomization, defined as mortality or hospitalization for CHF. Indeed, the administration of tolvaptan resulted in a greater, non-dose-dependent, net volume reduction compared with placebo and standard therapy including diuretics (–1.80, –2.10, –2.05 and –0.60 kg for the groups receiving tolvaptan 30, 60, 90 mg and placebo, respectively; p = 0.002, 0.002 and 0.009 for the 3 tolvaptan groups versus placebo). Furthermore, tolvaptan produced a rapid and sustained increase of serum sodium levels in patients with hyponatremia. There were no significant differences in the second primary endpoint at 60 days in patients receiving tolvaptan compared with placebo. The post hoc analysis revealed a lower 60-day mortality rate in patients with severe renal dysfunction or systemic congestion.

Particularly the latter finding suggested the favourable effect of tolvaptan on hemodynamic parameters in CHF, which was examined in the METEOR study [47]. The objective of this trial was to test the effects of intermediate-term therapy with tolvaptan on both LV dilatation and function (remodelling) and also on safety and tolerability in patients with CHF and LV systolic dysfunction. Eligible patients (n=240) with mild-to-moderate CHF (NYHA II or III), LV ejection fraction (LVEF) ≤30% were randomized to tolvaptan 30 mg/d or placebo. However, no significant effect of tolvaptan therapy was seen on LV volume or LVEF observed after 1 year of therapy.

The clinical applicability of tolvaptan was further evaluated in a pivotal EVEREST trial program [48]. The prospective, multicenter, double-blind, placebo-controlled EVEREST studies tested the benefit of single-dose tolvaptan (30 mg/d) versus placebo in 3 clinical trials: 2 short-term trials and a longer-term safety and outcome trial. A total of 4133 patients with

systolic dysfunction (LVEF <40%, NYHA III/IV) and hospitalized for ADHF CHF were randomized. The primary endpoint of the short-term trials was a composite of changes in patient-assessed global clinical status and body weight at 7 days or the day of discharge from hospital. The primary endpoints of the longer-term trial were all-cause mortality, cardiovascular death or CHF hospitalization.

In both short-term trials, the addition of tolvaptan to standard therapy resulted in a significant improvement of global clinical status and body weight change at day 7 or at discharge. When the composite outcomes were considered individually (as secondary outcomes), there was statistical benefit for tolvaptan-induced reductions in body weight in both trials on day 1 and day 7 ($p<0.001$ for all comparisons). There were no significant differences in patient-assessed global clinical status in either trial.

The longer-term trial demonstrated no differences in all-cause mortality, cardiovascular death or CHF-related hospitalization between the groups. In the subgroup of patients with hyponatremia (serum sodium <134 mmol/l) at baseline, there was a significantly greater increase in mean serum sodium levels from baseline to day 7 in the tolvaptan group than in the placebo group (increase of 5.49 mmol/l versus 1.85 mmol/l; $p<0.001$). This effect was maintained through 40 weeks of treatment.

Overall, the findings from EVEREST trials evidenced that tolvaptan produced early and sustainable decrease in body weight in patients hospitalized with worsening CHF and LVEF <30%, ameliorated dyspnea and edema, improved serum sodium in hyponatremic patients. Tolvaptan had no effect on global clinical condition, post-discharge mortality and hospitalization without evidence of harm.

In the following ECLIPSE study a total of 181 patients with advanced CHF (NYHA class III/IV CHF, LVEF <40% and pulmonary capillary wedge pressure (PCWP) >18 mmHg) were randomized to double-blind treatment with tolvaptan at a single oral dose (15, 30 or 60 mg/d) or placebo [49]. Tolvaptan at all doses significantly reduced PCWP, right atrial and

pulmonary artery pressure. Additionally, tolvaptan significantly increased urine output in a dose-dependent manner, without changes in renal function.

Liver cirrhosis. In a Japanese multicenter, open-label, dose-ranging study tolvaptan was orally administrated at titrated doses of 15, 30, and 60 mg once daily for 3 days at each dose to 18 liver cirrhosis patients with persistent ascites and/or lower limb edema despite receiving oral furosemide at 40 mg/day or higher [50]. It could be shown that tolvaptan dose-dependently decreased body weight (-1.6 ± 0.9, -2.6 ± 1.2 and -3.4 ± 2.1 kg) and abdominal circumference (-2.8 to -6.0 cm) and improved ascites and edema beginning from 15 mg, demonstrating a potent aquaretic effect.

Cirrhosis and SIADH. The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT trial) assessed the effects of tolvaptan in patients with hyponatremia. 448 patients with hyponatremia due to SIADH, CHF or cirrhosis were treated either with tolvaptan or placebo for 30 days [51]. Primary end-points were changes in serum sodium concentration at 4 and 30 days of therapy. The administration of tolvaptan was associated with a marked and significant increase in the area under the concentration time profile of serum sodium at days 4 ($p<0.001$) and 30 ($p<0.001$) compared to placebo. The number of patients with normal serum sodium concentration at the end of therapy was markedly higher in the tolvaptan compared to the placebo group (55% versus 25%, respectively). The effect of the drug on serum sodium concentration was observed both in patients with mild and severe hyponatremia.

In the SALTWATER trial, a multicenter, open-label extension of the SALT trial, 111 patients with hyponatremia received oral tolvaptan for a mean follow-up of 701 days. All patients had hyponatremia at randomization in the SALT study, and 85% continued to have hyponatremia at baseline when entering the SALTWATER study. The mean sodium increased from 130.8 mmol/l at baseline to >135 mmol/l throughout the observation period. It was shown that long-term treatment with tolvaptan was safe and efficient. Hypernatremia (>145 mmol/l) and subsequent discontinuation of the treatment occurred in one patient. The most common

adverse effects of tolvaptan were pollakisuria, thirst, fatigue, dry mouth, polydipsia and polyuria [52].

Lixivaptan

Lixivaptan is a potent, orally active, non-peptide V_2R-selective antagonist. Lixivaptan inhibits AVP binding to the V_{1a}R with an IC_{50} of 230 nM and to the V_2R with an IC_{50} of 1.2±0.1 nM [53]. Furthermore, lixivaptan has higher affinity for the V_2R than other AVP receptor antagonists, as demonstrated in human and rat studies [53, 54]. Lixivaptan is currently undergoing Phase III clinical trials to determine its possible role in the treatment of hyponatremia assosciated with CHF, cirrhosis and SIADH. The dosage used in clinical trials ranged from 10 mg/d to a maximal daily dose of 400 mg.

The major side effects were reported at higher doses (>200 mg/d) including excessive thirst, hypotension, hypernatremia and dehydration.

CHF. The therapeutic potential of different doses of lixivaptan was evaluated in 42 patients with mild-to-moderate CHF (NYHA II/III) in a randomized, double-blind, placebo-controlled, single-dose study [55]. Lixivaptan caused significant and dose-dependent increase in urine volume and solute-free water excretion at all doses except the 10 mg. At doses > 75 mg, serum sodium was significantly increased within the normal range. During 24 h, increases in urine volume ranged from 1.8 l with placebo to 3.9 l after the 400 mg lixivaptan dose ($p < 0.01$). Furthermore, no neurohormonal changes or any serious adverse events were reported during the use of lixivaptan. Unfortunately, clinical outcomes, such as dyspnea or global clinical status, were not assessed in the study.

In February 2008, a Phase III study known as the BALANCE trial (Treatment of Hyponatremia BAsed on LixivAptan in NYHA class III/IV Cardiac patient Evaluation) was initiated. The purpose of this ongoing multi-center, randomized, placebo-controlled, double-blind study is to determine the safety and efficacy of lixivaptan in the treatment of

hyponatremia in 650 patients with worsening CHF. Results of this trial would provide more insights into the lixivaptan's potential for treatment of CHF patients [56].

Liver cirrhosis/SIADH. The effect of lixivaptan has also been investigated in liver cirrhosis. A randomized double-blind multicenter trial assigned 60 patients with liver cirrhosis and dilutional hyponatremia to 100 or 200 mg/day of lixivaptan or placebo [57]. Normalization of serum sodium concentration was achieved in 27% and 50% of patients in the lixivaptan 100 mg/d and 200 mg/d groups, respectively, but in none of the patients in the placebo group. The treatment was also associated with a significant reduction in urine osmolality and body weight.

Another randomized, double-blind, placebo-controlled trial investigated the pharmacodynamic effects of lixivaptan with different doses in cirrhotic patients with ascites [58]. Here again, lixivaptan produced a significant dose-related increase in daily urine output and a dose-related decrease in urine osmolality.

Data for the efficacy of lixivaptan in the treatment of SIADH were obtained mostly in studies including patients with liver cirrhosis and/or CHF such as the study by Wong et al. who investigated the effect of lixivaptan in 3 different doses (25 mg, 125 mg and 250 mg) twice daily or placebo in patients with cirrhosis (n=33), CHF (n=6) and SIADH (n=5) [59]. Lixivaptan produced a significant overall aquaretic response compared with placebo, with significant dose-related increases in free water clearance ($p<0.05$) and serum sodium ($p<0.05$), without significant changes in orthostatic blood pressure or serum creatinine levels.

Another smaller study looking at the evolution hyponatremia in SIADH and liver cirrhosis after treatment with lixivaptan was conducted by [60]. Here, 6 hyponatremic patients with SIADH and 5 hyponatremic patients with cirrhosis and ascites were treated with 50 or 100 mg lixivaptan twice daily. In patients with SIADH treated with lixivaptan, serum sodium concentration was generally corrected in 1 day (126 ± 4.5 mmol/l at 0 hours and 133 ± 5.6 mmol/l at 24 hours) and associated with a decrease in sodium excretion (from 82 ± 22

mmol/24 hours to 45 ± 21 mmol/24 hours; $p<0.05$) without modification in potassium excretion, suggesting that lixivaptan is a highly effective drug in the short-term management of hyponatremic patients with SIADH.

Satavaptan

Satavaptan is an AVP receptor antagonist with enhanced affinity to V_2R compared to $V_{1a}R$ [61, 62]. Thus, satavaptan inhibits AVP binding to the human V_2R with a K_i of 4.1 ± 0.8 nM; the respective K_i for $V_{1a}R$ and $V_{1b}R$ were 460 ± 120 nM and >10.000 nM [63]. Satavaptan was intended to be used for the treatment of euvolaemic and hypervolaemic hyponatraemia and was therefore under regulatory review in the European Union. However, the application for a centralised marketing authorisation for the satavaptan 5 mg and 25 mg was withdrawn by the developing company in May 2008 likely due to poorer survival in the satavaptan-treated patients in a SPARe-1 trial (results are not published to date).

Maximal plasma concentrations of the substance were observed 3h after administration; mean plasma concentration increased with dosage and duration of drug application and stabilized on day 5. The major route of excretion was via feces [62]. Satavaptan is available as an oral preparation at 5-50 mg dosages; the aquaretic effect following the drug administration persists up to 12 hours [64].

The efficacy of satavaptan was first evaluated in the phase II trial in patients with hyponatremia due to SIADH [65]. Satavaptan was well tolerated in clinical trials; the main adverse effects associated with the use of satavaptan included increased thirst and dry mouth.

CHF. Although the agent has demonstrated utility in animal models and improved clinical outcomes in patients with SIADH or cirrhosis [65-68], its efficacy in CHF patients has yet to be determined.

Liver cirrhosis. In a randomized double-blind study on 150 cirrhotic patients with recurrent ascites with or without hyponatremia, satavaptan showed the potential to reduce recurrence of

ascites after large volume paracentesis [69]. Three different doses of satavaptan (5, 12.5, and 25 mg/d) and a placebo were given to hypo- or normonatremic cirrhotic patients with ascites, which periodically required large volume paracentesis. All subjects also received spironolactone (100 mg/d). The main endpoints of the study were the length of the interval between two consecutive paracentesis and the weekly amount of ascites accumulation estimated by summing up the litres of ascites removed with paracentesis and by following the changes in kilograms of body weight. A secondary endpoint was the total number of paracentesis performed during 12 weeks of treatment. The trial was based on the rationale that increasing the urine volume by antagonizing the renal AVP effects can delay the recurrence of ascites after paracentesis. Indeed, satavaptan significantly ($p<0.05$) reduced the frequency of large volume paracentesis over a 3-month period in cirrhotic patients with recurrent ascites and was well tolerated. Mean increase in ascites was 2.82 ± 0.48 l/week for placebo versus 2.12 ± 0.40, 2.14 ± 0.33 and 2.06 ± 0.40 l/week for the 5, 12.5 and 25 mg of satavaptan, respectively (p= NS for all doses).

The clinical applicability of satavaptan in the case of liver cirrhosis with hyponatremia was further assessed in the short-term HypoCATtrial [67]. The multicenter, double-blind, randomized, controlled study compared three fixed doses of satavaptan (5 mg, 12.5 mg, or 25 mg once daily) versus placebo in 110 patients with cirrhosis, and hyponatremia (serum sodium ≤ 130 mmol/L). Duration of treatment was 14 days and all patients received spironolactone at 100 mg/day. Satavaptan treatment was associated with improved control of ascites, as indicated by a reduction in body weight and a parallel reduction in abdominal girth. This beneficial effect on ascites was associated with improvements in serum sodium (mean change from baseline to day 5 was 1.3 ± 4.2, 4.5 ± 3.5, 4.5 ± 4.8 and 6.6 ± 4.3 mmol/l for placebo and satavaptan 5, 12.5 and 25 mg/day, respectively; $p<0.01$ for all compared to placebo).

Thirst was significantly more common in patients treated with satavaptan compared to those treated with placebo, whereas the frequency of other adverse events was similar among groups.

SIADH. Soupart et al. studied in a first part of a randomized, double-blind and placebo-controlled study the effect of satavaptan in 34 patients with hyponatremia due to SIADH [65]. The substance was shown to be effective in increasing serum sodium in 79% patients receiving 25 mg dose and 83% of patients treated with 50 mg substance in contrast to 13% of patients treated with placebo. Furthermore satavaptan maintained efficiently serum sodium levels without serious adverse events during the long-term treatment in the following open label trial, suggesting that satavaptan adequately corrects mild or moderate hyponatremia in patients with SIADH.

In conclusion, satavaptan is a potent antagonist of the renal AVP effects that, in combination with diuretics, might play a role in the treatment of recurrent or refractory ascites, as well as in the correction of hyponatremia.

Combined V_{1a}/V_2R antagonists

Conivaptan

Conivaptan is currently the only available dual V_{1a}/V_2R antagonist with *in vitro* binding affinities (K_i) of 6.30 nmol/L and 1.10 nmol/L for human $V_{1a}R$ and V_2R, respectively [70].

Conivaptan is available for i.v. application and was the first AVP receptor antagonist to be approved by FDA for treatment of euvolemic hyponatraemia. Since 2007 conivaptan is approved also for hypervolemic hyponatraemia. At present, conivaptan is not indicated for primary treatment of CHF. Conivaptan is approved for use in hospitalized patients with an initial loading dose of 20 mg i.v. over 30 min followed by 20 mg (max. 40 mg) continuous infusion over the next 24 hours. The duration of continuous treatment should not exceed 4 days.

Conivaptan is metabolized by the CYP3A4 [71]. Due to its interaction with CYP3A4 the coadministration of conivaptan with potent CYP3A4 inhibitors such as clarithromycin, itraconazol, ketoconazole, ritonavir is contraindicated. Approximately 83% of the substance is excreted in the feces and 12% in the urine [71, 72]. In clinical trials conivaptan was generally well tolerated. The most reported adverse side effects are local injection site reactions, headache and thirst. Caution should be exercised in patients with renal or liver impairment.

Pharmacologically, because of its dual V_{1a}/V_2R antagonism conivaptan represents an excellent option for the treatment of CHF. Consistently, conivaptan has demonstrated efficacy in animal models of altered cardiac function and volume overload. Intravenous administration of conivaptan was shown to produce hemodynamic improvement and marked aquaresis in a canine model of CHF induced by rapid right ventricular pacing [73].

Despite these encouraging animal data, human clinical evidence remains inconsistent. In a double-blind and placebo-controlled study of 142 patients with advanced CHF conivaptan (10, 20 or 40 mg i.v.) produced favorable hemodynamic and renal effects. Decreases in PCWP (-2.6 ± 0.7, -5.4 ± 0.7 and -4.6 ± 0.7 mmHg for placebo and 20 and 40 mg groups, respectively; $p<0.05$) and right atrial pressure (-2.0 ± 0.4, -3.7 ± 0.4 and -3.5 ± 0.4 mmHg for placebo and 20 and 40 mg groups, respectively; $p<0.05$) were accompanied by substantial increases in urine output (-11 ± 17, 68 ± 17, 152 ± 19 and 176 ± 18 ml/hour for placebo and 10, 20 and 40 mg groups, respectively; $p<0.001$), without affecting cardiac index, systemic and pulmonary vascular resistance, blood pressure, heart rate or serum electrolytes [74].

In the double-blind, placebo-controlled ADVANCE (A Dose evaluation of a Vasopressin Antagonist in CHF patients undergoing Exercise) study the effect of 12-week conivaptan treatment (10, 20 and 40 mg/d) was assessed in 343 patients with moderate-to-severe CHF [75]. However, conivaptan treatment was not associated with a significant improvement in overall functional capacity, exercise tolerance and quality of life in these patients.

The potential therapeutic benefit of conivaptan in patients with CHF prompted another pilot study to evaluate the efficacy and safety of conivaptan (20 mg loading dose followed by 24-hour continuous infusions of 40, 80 or 120 mg/d) in alleviating the signs and symptoms of congestion in patients with ADHF [76]. Conivaptan at each dosage increased urine output significantly more than placebo at 24 hours ($p \leq 0.02$), with the difference averaging 1 to 1.5 l. The decreases in body weight with conivaptan 40 and 80 mg/d ranged from 0.7 to 2 kg greater than with placebo (p=NS) without any overall improvement of clinical status and was well tolerated in patients with ADHF.

Despite being well tolerated and able to significantly increase urine output, the precise role of conivaptan in CHF remains to be defined. In this respect, it should be emphasized that the FDA approvement is still restricted for the treatment of euvolemic hyponatremia.

Liver cirrhosis. In the case of liver cirrhosis, so far conivaptan has been mainly assessed in animal studies. One of these studies addressed the effect of conivaptan on renal water metabolism and systemic hemodynamics in rats with cirrhosis and ascites [77]. In this case, cirrhotic rats treated with conivaptan no longer showed any hyponatremia or water retention.

SIADH. There is paucity of reported clinical experience using conivaptan for the treatment of the SIADH. Recently a single-center study conducted by Velez et al. assessed retrospectively the effect of intravenous conivaptan as an aquaretic in 18 patients with SIADH [78].

67% patients reached the primary end point of the study defined as an absolute increase of ≥ 4 mmol/l sodium over baseline 24 hours after initiation of therapy. Additionally, all patients had at least a 3-mmol/L increase in serum sodium 24 hours after therapy initiation (mean baseline serum sodium of 121.7 ± 3.3 mmol/l versus 129.2 ± 2.6 mmol/l at 24 hours, $p < 0.001$). Increase in serum sodium was sustained at 48 and 72 hours (129.6 ± 2.4 and 130.5 ± 2.5 mmol/l, respectively; $p < 0.001$). At the same time urine osmolality decreased in all patients. Lower serum sodium, lower blood urea nitrogen and higher

estimated glomerular filtration rate at baseline had a significant correlation with the magnitude of the absolute increase in serum sodium 24 hours after initiation of therapy, suggesting that these variables may also help predicting the magnitude of response to therapy.

Conclusions

Over the last years, several randomized clinical trials assessed the efficacy and safety of vasopressin-receptor antagonists in water-retentive disorders such as CHF, SIADH and liver cirrhosis.

CHF, liver cirrhosis and SIADH remain a major health concern. Existing therapeutic options only slow the progression of CHF or cirrhosis, thus warranting the search for novel therapeutic approaches. In both acute and chronic CHF as well as in liver cirrhosis and SIADH, plasma AVP levels are inappropriately high and correlate with poor outcome. AVP has adverse effects by increasing peripheral resistance via vasoconstrictor actions at the $V_{1a}R$ and contributing to water retention through effects at the renal V_2R. Based on the pathophysiological mechanisms and experimental data, V_2R and especially combined V_{1a}/V_2R antagonists offer an excellent therapeutic option in CHF by serving as aquaretics and improving hemodynamic parameters. Although the animal data were promising, AVP receptor antagonists have shown only modest benefits in patients with CHF in clinical trials. So far, no mortality or morbidity benefits were demonstrated for AVP antagonists in congestive heart disease. In the case of liver cirrhosis and SIADH, long-term data regarding efficacy and safety of vaptans are still missing.

Unanswered questions are whether AVP receptor antagonists are superior to existing therapies, whether they truly have effects beyond the correction of hyponatremia and what the advantages or disadvantages are of combined V_{1a}/V_2R antagonism. Because data on long-term administration are still incomplete, they cannot yet be used routinely.

Therefore, more clinical evidence is needed to establish the role of vaptans in the treatment of CHF, liver cirrhosis and SIADH. Obtaining this information will be necessary in order to evaluate the risk/benefit ratio for the chronic use of vaptans outside randomized clinical trials.

Conflict of interest: The authors declare that they have no conflicts of interest relevant to the manuscript.

References

1 Goldsmith SR (1988) Baroreceptor-mediated suppression of osmotically stimulated vasopressin in normal humans. J Appl Physiol 65 (3): 1226-1230

2 Robertson GL, Shelton RL, Athar S (1976) The osmoregulation of vasopressin. Kidney Int 10 (1): 25-37

3 Schrier RW, Berl T, Anderson RJ (1979) Osmotic and nonosmotic control of vasopressin release. Am J Physiol 236 (4): F321-332

4 Schweiger TA, Zdanowicz MM (2008) Vasopressin-receptor antagonists in heart failure. Am J Health Syst Pharm 65 (9): 807-817

5 Laugwitz KL, Ungerer M, Schoneberg T, Weig HJ, Kronsbein K, Moretti A, Hoffmann K, Seyfarth M, Schultz G, Schomig A (1999) Adenoviral gene transfer of the human V2 vasopressin receptor improves contractile force of rat cardiomyocytes. Circulation 99 (7): 925-933

6 Kaufmann JE, Iezzi M, Vischer UM (2003) Desmopressin (DDAVP) induces NO production in human endothelial cells via V2 receptor- and cAMP-mediated signaling. J Thromb Haemost 1 (4): 821-828

7 Kaufmann JE, Oksche A, Wollheim CB, Gunther G, Rosenthal W, Vischer UM (2000) Vasopressin-induced von Willebrand factor secretion from endothelial cells involves V2 receptors and cAMP. J Clin Invest 106 (1): 107-116

8 Bernat A, Hoffmann P, Dumas A, Serradeil-le Gal C, Raufaste D, Herbert JM (1997) V2 receptor antagonism of DDAVP-induced release of hemostasis factors in conscious dogs. J Pharmacol Exp Ther 282 (2): 597-602

9 Nielsen S, Frokiaer J, Marples D, Kwon TH, Agre P, Knepper MA (2002) Aquaporins in the kidney: from molecules to medicine. Physiol Rev 82 (1): 205-244

10 Ali F, Guglin M, Vaitkevicius P, Ghali JK (2007) Therapeutic potential of vasopressin receptor antagonists. Drugs 67 (6): 847-858

11 Folny V, Raufaste D, Lukovic L, Pouzet B, Rochard P, Pascal M, Serradeil-Le Gal C (2003) Pancreatic vasopressin V1b receptors: characterization in In-R1-G9 cells and localization in human pancreas. Am J Physiol Endocrinol Metab 285 (3): E566-576

12 Gassanov N, Jankowski M, Danalache B, Wang D, Grygorczyk R, Hoppe UC, Gutkowska J (2007) Arginine vasopressin-mediated cardiac differentiation: insights into the role of its receptors and nitric oxide signaling. J Biol Chem 282 (15): 11255-11265

13 Goldsmith SR, Gheorghiade M (2005) Vasopressin antagonism in heart failure. J Am Coll Cardiol 46 (10): 1785-1791

14 Goldsmith SR, Francis GS, Cowley AW, Jr., Levine TB, Cohn JN (1983) Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1 (6): 1385-1390

15 Pacher R, Stanek B, Hulsmann M, Koller-Strametz J, Berger R, Schuller M, Hartter E, Ogris E, Frey B, Heinz G, Maurer G (1996) Prognostic impact of big endothelin-1 plasma concentrations compared with invasive hemodynamic evaluation in severe heart failure. J Am Coll Cardiol 27 (3): 633-641

16 Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW (1981) Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med 305 (5): 263-266

17 Edwards BS, Zimmerman RS, Burnett JC, Jr. (1987) Atrial natriuretic factor: physiologic actions and implications in congestive heart failure. Cardiovasc Drugs Ther 1 (1): 89-100

18 Habib F, Dutka D, Crossman D, Oakley CM, Cleland JG (1994) Enhanced basal nitric oxide production in heart failure: another failed counter-regulatory vasodilator mechanism? Lancet 344 (8919): 371-373
19 Kalra PR, Anker SD, Coats AJ (2001) Water and sodium regulation in chronic heart failure: the role of natriuretic peptides and vasopressin. Cardiovasc Res 51 (3): 495-509
20 Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ (1999) Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 100 (12): 1311-1315
21 McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC (2004) Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 44 (6): 1301-1307
22 Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S (1990) Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 82 (5): 1724-1729
23 Rossi GP (2007) Arginine vasopressin receptor antagonists for heart failure: a winter climbing to the Everest's tip? J Am Coll Cardiol 49 (22): 2160-2162
24 Arnolda L, McGrath BP, Johnston CI (1991) Systemic and regional effects of vasopressin and angiotensin in acute left ventricular failure. Am J Physiol 260 (2 Pt 2): H499-506
25 Burrell LM, Phillips PA, Risvanis J, Chan RK, Aldred KL, Johnston CI (1998) Long-term effects of nonpeptide vasopressin V2 antagonist OPC-31260 in heart failure in the rat. Am J Physiol 275 (1 Pt 2): H176-182
26 Nakamura Y, Haneda T, Osaki J, Miyata S, Kikuchi K (2000) Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin V(1A) receptor. Eur J Pharmacol 391 (1-2): 39-48
27 Gines P, Arroyo V, Rodes J (1998) Ascites and hepatorenal syndrome: pathogenesis and treatment strategies. Adv Intern Med 43: 99-142
28 Ferguson JW, Therapondos G, Newby DE, Hayes PC (2003) Therapeutic role of vasopressin receptor antagonism in patients with liver cirrhosis. Clin Sci (Lond) 105 (1): 1-8 DOI 10.1042/CS20030062
CS20030062 [pii]
29 Bichet D, Szatalowicz V, Chaimovitz C, Schrier RW (1982) Role of vasopressin in abnormal water excretion in cirrhotic patients. Ann Intern Med 96 (4): 413-417
30 Bichet DG, Van Putten VJ, Schrier RW (1982) Potential role of increased sympathetic activity in impaired sodium and water excretion in cirrhosis. N Engl J Med 307 (25): 1552-1557 DOI 10.1056/NEJM198212163072504
31 Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA (2004) Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 40 (4): 802-810 DOI 10.1002/hep.20405
32 Berghmans T, Paesmans M, Body JJ (2000) A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer 8 (3): 192-197
33 Baylis PH (2003) The syndrome of inappropriate antidiuretic hormone secretion. Int J Biochem Cell Biol 35 (11): 1495-1499 DOI S1357272503001390 [pii]
34 Vanhees SL, Paridaens R, Vansteenkiste JF (2000) Syndrome of inappropriate antidiuretic hormone associated with chemotherapy-induced tumour lysis in small-cell lung cancer: case report and literature review. Ann Oncol 11 (8): 1061-1065

35 Miller M (2001) Syndromes of excess antidiuretic hormone release. Crit Care Clin 17 (1): 11-23, v
36 Casulari LA, Costa KN, Albuquerque RC, Naves LA, Suzuki K, Domingues L (2004) Differential diagnosis and treatment of hyponatremia following pituitary surgery. J Neurosurg Sci 48 (1): 11-18
37 Oh MS (2002) Pathogenesis and diagnosis of hyponatremia. Nephron 92 Suppl 1: 2-8 DOI nef2a002 [pii]
38 Sawyer WH, Pang PK, Seto J, McEnroe M, Lammek B, Manning M (1981) Vasopressin analogs that antagonize antidiuretic responses by rats to the antidiuretic hormone. Science 212 (4490): 49-51
39 Yamamura Y, Ogawa H, Yamashita H, Chihara T, Miyamoto H, Nakamura S, Onogawa T, Yamashita T, Hosokawa T, Mori T, et al. (1992) Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V2 receptor antagonist. Br J Pharmacol 105 (4): 787-791
40 Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, Yamashita T, Yamada Y, Tsujimae K, Aoyama M, Kotosai K, Ogawa H, Yamashita H, Kondo K, Tominaga M, Tsujimoto G, Mori T (1998) OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther 287 (3): 860-867
41 Rangasetty UC, Gheorghiade M, Uretsky BF, Orlandi C, Barbagelata A (2006) Tolvaptan: a selective vasopressin type 2 receptor antagonist in congestive heart failure. Expert Opin Investig Drugs 15 (5): 533-540 DOI 10.1517/13543784.15.5.533
42 Shoaf SE, Elizari MV, Wang Z, Sekar K, Grinfeld LR, Barbagelata NA, Lerman J, Bramer SL, Tronge J, Orlandi C (2005) Tolvaptan administration does not affect steady state amiodarone concentrations in patients with cardiac arrhythmias. J Cardiovasc Pharmacol Ther 10 (3): 165-171
43 Shoaf SE, Wang Z, Bricmont P, Mallikaarjun S (2007) Pharmacokinetics, pharmacodynamics, and safety of tolvaptan, a nonpeptide AVP antagonist, during ascending single-dose studies in healthy subjects. J Clin Pharmacol 47 (12): 1498-1507 DOI 0091270007307877 [pii]
10.1177/0091270007307877
44 Plosker GL (2010) Tolvaptan. Drugs 70 (4): 443-454 DOI 10.2165/11204630-000000000-00000
5 [pii]
45 Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, Orlandi C (2003) Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 107 (21): 2690-2696
46 Gheorghiade M, Gattis WA, O'Connor CM, Adams KF, Jr., Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C (2004) Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. Jama 291 (16): 1963-1971
47 Udelson JE, McGrew FA, Flores E, Ibrahim H, Katz S, Koshkarian G, O'Brien T, Kronenberg MW, Zimmer C, Orlandi C, Konstam MA (2007) Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. J Am Coll Cardiol 49 (22): 2151-2159
48 Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C (2007) Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. Jama 297 (12): 1319-1331

49 Udelson JE, Orlandi C, Ouyang J, Krasa H, Zimmer CA, Frivold G, Haught WH, Meymandi S, Macarie C, Raef D, Wedge P, Konstam MA, Gheorghiade M (2008) Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: an international, multicenter, randomized, placebo-controlled trial. J Am Coll Cardiol 52 (19): 1540-1545

50 Okita K, Sakaida I, Okada M, Kaneko A, Chayama K, Kato M, Sata M, Yoshihara N, Ono N, Murawaki Y (2010) A multicenter, open-label, dose-ranging study to exploratively evaluate the efficacy, safety, and dose-response of tolvaptan in patients with decompensated liver cirrhosis. J Gastroenterol 45 (9): 979-987 DOI 10.1007/s00535-010-0240-6

51 Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C (2006) Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 355 (20): 2099-2112

52 Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS (2010) Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 21 (4): 705-712 DOI ASN.2009080857 [pii]
10.1681/ASN.2009080857

53 Albright JD, Reich MF, Delos Santos EG, Dusza JP, Sum FW, Venkatesan AM, Coupet J, Chan PS, Ru X, Mazandarani H, Bailey T (1998) 5-Fluoro-2-methyl-N-[4-(5H-pyrrolo[2,1-c]-[1, 4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]benzamide (VPA-985): an orally active arginine vasopressin antagonist with selectivity for V2 receptors. J Med Chem 41 (14): 2442-2444

54 Chan PS, Coupet J, Park HC, Lai F, Hartupee D, Cervoni P, Dusza JP, Albright JD, Ru X, Mazandarani H, Tanikella T, Shepherd C, Ochalski L, Bailey T, Lock TY, Ning X, Taylor JR, Spinelli W (1998) VPA-985, a nonpeptide orally active and selective vasopressin V2 receptor antagonist. Adv Exp Med Biol 449: 439-443

55 Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW (2006) Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. J Am Coll Cardiol 47 (8): 1615-1621

56 Abraham WT, Aranda JM, Boehmer JP, Elkayam U, Gilbert EM, Gottlieb SS, Hasenfubeta G, Kukin M, Lowes BD, O'Connell JB, Tavazzi L, Feldman AM, Ticho B, Orlandi C (2010) Rationale and Design of the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (THE BALANCE) Study. Clin Transl Sci 3 (5): 249-253 DOI 10.1111/j.1752-8062.2010.00217.x

57 Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, Djian J (2003) Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 124 (4): 933-939 DOI 10.1053/gast.2003.50143
S001650850300057X [pii]

58 Guyader D, Patat A, Ellis-Grosse EJ, Orczyk GP (2002) Pharmacodynamic effects of a nonpeptide antidiuretic hormone V2 antagonist in cirrhotic patients with ascites. Hepatology 36 (5): 1197-1205 DOI 10.1053/jhep.2002.36375
S0270913902001386 [pii]

59 Wong F, Blei AT, Blendis LM, Thuluvath PJ (2003) A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology 37 (1): 182-191 DOI 10.1053/jhep.2003.50021
S0270913902141358 [pii]

60 Decaux G (2001) Difference in solute excretion during correction of hyponatremic patients with cirrhosis or syndrome of inappropriate secretion of antidiuretic hormone by oral vasopressin V2 receptor antagonist VPA-985. J Lab Clin Med 138 (1): 18-21 DOI S0022-2143(01)42759-4 [pii]
10.1067/mlc.2001.116025
61 Gross P, Reimann D, Henschkowski J, Damian M (2001) Treatment of severe hyponatremia: conventional and novel aspects. J Am Soc Nephrol 12 Suppl 17: S10-14
62 Costello-Boerrigter LC, Boerrigter G, Burnett JC, Jr. (2009) Pharmacology of vasopressin antagonists. Heart Fail Rev 14 (2): 75-82 DOI 10.1007/s10741-008-9108-8
63 Serradeil-Le Gal C, Lacour C, Valette G, Garcia G, Foulon L, Galindo G, Bankir L, Pouzet B, Guillon G, Barberis C, Chicot D, Jard S, Vilain P, Garcia C, Marty E, Raufaste D, Brossard G, Nisato D, Maffrand JP, Le Fur G (1996) Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. J Clin Invest 98 (12): 2729-2738 DOI 10.1172/JCI119098
64 Palm C, Pistrosch F, Herbrig K, Gross P (2006) Vasopressin antagonists as aquaretic agents for the treatment of hyponatremia. Am J Med 119 (7 Suppl 1): S87-92
65 Soupart A, Gross P, Legros JJ, Alfoldi S, Annane D, Heshmati HM, Decaux G (2006) Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V2-receptor antagonist. Clin J Am Soc Nephrol 1 (6): 1154-1160
66 Bishara B, Shiekh H, Karram T, Rubinstein I, Azzam ZS, Abu-Saleh N, Nitecki S, Winaver J, Hoffman A, Abassi ZA (2008) Effects of novel vasopressin receptor antagonists on renal function and cardiac hypertrophy in rats with experimental congestive heart failure. J Pharmacol Exp Ther 326 (2): 414-422
67 Gines P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D (2008) Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. Hepatology 48 (1): 204-213
68 Gines P, Wong F, Watson H, Terg R, Bruha R, Zarski JP, Dudley F Clinical trial: short-term effects of combination of satavaptan, a selective vasopressin V2 receptor antagonist, and diuretics on ascites in patients with cirrhosis without hyponatraemia--a randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 31 (8): 834-845
69 Wong F, Gines P, Watson H, Horsmans Y, Angeli P, Gow P, Minini P, Bernardi M (2010) Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. J Hepatol 53 (2): 283-290 DOI S0168-8278(10)00381-8 [pii]
10.1016/j.jhep.2010.02.036
70 Tahara A, Saito M, Sugimoto T, Tomura Y, Wada K, Kusayama T, Tsukada J, Ishii N, Yatsu T, Uchida W, Tanaka A (1998) Pharmacological characterization of YM087, a potent, nonpeptide human vasopressin V1A and V2 receptor antagonist. Naunyn Schmiedebergs Arch Pharmacol 357 (1): 63-69
71 Hoque MZ, Arumugham P, Huda N, Verma N, Afiniwala M, Karia DH (2009) Conivaptan: promise of treatment in heart failure. Expert Opin Pharmacother 10 (13): 2161-2169 DOI 10.1517/14656560903173237
72 Finley JJt, Konstam MA, Udelson JE (2008) Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. Circulation 118 (4): 410-421

73 Yatsu T, Tomura Y, Tahara A, Wada K, Kusayama T, Tsukada J, Tokioka T, Uchida W, Inagaki O, Iizumi Y, Tanaka A, Honda K (1999) Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V1A and V2 receptor antagonist, in dogs with pacing-induced congestive heart failure. Eur J Pharmacol 376 (3): 239-246

74 Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, Ghali JK, Selaru P, Chanoine F, Pressler ML, Konstam MA (2001) Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 104 (20): 2417-2423

75 Russel S, Adams K, Shaw J (2003) Results of a twelve week double-blind,placebo-controlled, multicenter studyof oral conivaptan to assess functional
capacity in patients with class IIIchronic heart failure. 2003;9(suppl):S60. Abstract. J Card Fail9(suppl):S60 Abstract

76 Goldsmith SR, Elkayam U, Haught WH, Barve A, He W (2008) Efficacy and safety of the vasopressin V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure: a dose-ranging pilot study. J Card Fail 14 (8): 641-647

77 Fernandez-Varo G, Ros J, Cejudo-Martin P, Cano C, Arroyo V, Rivera F, Rodes J, Jimenez W (2003) Effect of the V1a/V2-AVP receptor antagonist, Conivaptan, on renal water metabolism and systemic hemodynamics in rats with cirrhosis and ascites. J Hepatol 38 (6): 755-761 DOI S0168827803001168 [pii]

78 Velez JC, Dopson SJ, Sanders DS, Delay TA, Arthur JM (2010) Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience. Nephrol Dial Transplant 25 (5): 1524-1531 DOI gfp731 [pii]
10.1093/ndt/gfp731

79 Wong F, Gines P, Watson H, Horsmans Y, Angeli P, Gow P, Minini P, Bernardi M Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. J Hepatol 53 (2): 283-290

80 Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N (2007) Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol 27 (5): 447-457

Figure legends

Figure 1. Regulation of AVP secretion. Osmotic and non-osmotic triggers of AVP stimulation.

Figure 2. AVP receptors, their location and mediated effects. PLC, phospholipase C; ACTH , adrenocorticotropin; IP3 , phosphoinositol.

Figure 3. AVP-mediated effects in heart failure worsen heart failure symptoms and cardiac function.

Figure 4. Differentiation between euvolemic and hypervolemic hyponatremia. Hyponatremia is classified into three major categories based on plasma osmolality: normotone, hypertone and hypotone. Urine osmolality above 100 mosm/l along with the diminished urine sodium excretion (< 20 mmol/l) is typically found in patients with liver cirrhosis or CHF. In contrast, patients with SIADH exhibit hyperosmolalic urine with higher (> 40 mmol/l) urine sodium concentration.

Figure 5. Chemical structure of AVP receptor antagonists.

	Tolvaptan[40]	Lixivaptan[49,50]	Satavaptan[58]	Conivaptan[51,65,66]
Receptor specificity ($V_2R/V_{1a}R$)	29:1	100:1	112:1	1:6-10
Application route	oral	oral	oral	i.v.
Protein binding	99%	99%	88-90%	98.5%
Elimination half-life (h)	6-8	7-10	14-17	3.1-7.8
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Elimination	Faeces	Faeces	Faeces	Faeces
Dosage (mg/day)	15 (max. 60)	10-400*	5–50*	20 (max. 40)
Side effects	Pollakisuria, thirst, dry mouth, fatigue, polyuria and polydipsia	Thirst, hypotension, hypernatremia and dehydration (at doses >200 mg)	Increased thirst and dry mouth	local injection site reactions, headache and thirst
Clinical status	Approved 2008 by FDA for SIADH, CHF and cirrhosis; approved 2009 by EMEA for SIADH	Phase III	Unknown	Approved for euvolemic (2005) and hypervolemic (2007) hyponatremia by FDA

Table 1. Pharmacological properties of AVP receptor antagonists.

*Doses used in clinical trials

Reference	Patients characteristics and number (n)	Dosage	Outcomes
Tolvaptan			
Udelson et al. [47] (METEOR)	Patients with NYHA II-III, LVEF≤ 30% (n=240)	30 mg/d for 54 weeks	No significant changes in LVEDV/ EF after 1 year
Gheorghiade et al. [45]	Patients with CHF (n=254)	30, 45, 60 mg/d for 25 d	Decrease in body weight, increase in urine volume. Decrease in edema and increase of serum sodium in patients with hyponatremia
Udelson et al, [49] (ECLIPSE)	Patients with advanced CHF (n=181)	15, 30 or 60 mg single dose	Reduction in RAP, PCWP, PAP. Dose-dependent increase in urine output by 3h.
Gheorghiade et al [46] (ACTIV in CHF)	Patients with worsening CHF (n=319)	30, 60 or 90 mg/d for 60 d	Decrease in body weight, no differences in worsening CHF
Konstam et al, [48] EVEREST	Patients hospitalized for ADCHF with LVEF< 40% and NYHA III/IV (n=4133)	30 mg/d for a minimum of 60 d	Improvement in dyspnea, edema, body weight and mean serum sodium levels. No differences in long-term mortality or CHF-related morbidity.
Schrier et al, [51] SALT-trials	Patients with euvolemic or hypervolemic hyponatremia (n=448)	15 - 60 mg/d for 4 and 30 d	Increase in sodium levels at day 4 and 30
Lixivaptan			
Abraham et al, [55]	Patients with mild-to-moderate CHF (NYHA II/III, EF<35%) (n=42)	10, 30, 75, 150, 250 or 400 mg/d	Significant and dose-dependent increase in urine volume and solute-free water excretion
Satavaptan			
Wong et al, [79]	Cirrhotic patients with recurrent ascites (n=150)	5, 12.5 and 25 mg/d for 12 weeks	Reduction in frequency of large volume paracentesis
Soupart et al, [65]	Patients with hyponatremia due to SIADH (n=34)	25 and 50 mg/d for 12 months	Increase in serum sodium levels
Conivaptan			
Udelson et al, [74]	Short-term study in patients with advanced CHF (NYHA III-IV) (n=142)	10, 20 or 40 mg single i.v. dose	Increase in urine volume, reduction in PCWP and RAP during the first 3-6 h after drug application. No effect on CI, MAP, SVR. PVR, HR.
Goldsmith et al, [76]	Patients hospitalized for worsening CHF (n=170)	20-mg LD, then 24-hour 40, 80, or 120 mg/d i.v.	Increase in urine output, no change in global and respiratory status at 48 h
Zeltser et al, [80]	Patients with euvolemic or hypervolemic hyponatremia (serum sodium 115 - 130 mEq/l) (n=84)	20-mg LD, followed by a 96-hour infusion of 40 or 80 mg/d	Dose-dependent increase in serum sodium

Table 2. Selective randomized, double-blind and placebo-controlled clinical trials with vaptans. *LVEDV*, left ventricular enddiastolic volume; *RAP*, right atrial pressure; *PCWP*, pulmonary capillary wedge pressure; *CI*, cardiac index; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance; *PVR*, pulmonary vascular resistance; *HR*, heart rate; *LD*, loading dose.