LEADING ARTICLE

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Therapeutic Potential of Vasopressin Receptor Antagonists

Farhan Ali, *Maya Guglin*, *Peter Vaitkevicius* and *Jalal K. Ghali*

Heart Failure Program, Wayne State University, Detroit, Michigan, USA

Abstract

Arginine vasopressin (AVP) is a neuropeptide hormone that plays an important role in circulatory and sodium homeostasis, and regulating serum osmolality. Several clinical conditions have been associated with inappropriately elevated levels of AVP including heart failure, cirrhosis of the liver and the syndrome of inappropriate secretion of antidiuretic hormone. Three receptor subtypes that mediate the actions of AVP have been identified (V_{1A}, V_2 and V_{1B}).

Activation of V_{1A} receptors located in vascular smooth muscle cells and the myocardium results in vasoconstriction and increased afterload and hypertrophy. The V_2 receptors located primarily in the collecting tubules mediate free water absorption. The V_{1B} receptors are located in the anterior pituitary and mediate adrenocorticotropin hormone release.

The cardiovascular and renal effects of AVP are mediated primarily by V_{1A} and V_2 receptors. Antagonism of V_{1A} receptors results in vasodilatation and antagonism of V_2 receptors resulting in aquaresis, an electrolyte-sparing water excretion. Several non-peptide AVP antagonists (vasopressin receptor antagonists [VRAs]) also termed 'vaptans' have been developed and are vigorously being studied primarily for treating conditions characterised by hyponatraemia and fluid overload.

Conivaptan is a combined V_{1A}/V_2-receptor antagonist that induces diuresis as well as haemodynamic improvement. It has been shown in clinical trials to correct euvolaemic and hypervolaemic hyponatraemia, and has been approved by the US FDA for the treatment of euvolaemic hyponatraemia as an intravenous infusion. Tolvaptan, a selective V_2-receptor antagonist, has undergone extensive clinical studies in the treatment of hyponatraemia and heart failure. It has been shown to effectively decrease fluid in volume overloaded patients with heart failure and to correct hyponatraemia. A large outcome study (n = 4133 patients) will define its role in the management of heart failure. Lixivaptan and satavaptan (SR-121463) are other selective V_2-receptor antagonists being evaluated for the treatment of hyponatraemia.

In addition, a potential role for the vaptans in attenuating polyuria in nephrogenic diabetes insipidus and cyst development in polycystic kidney disease is being explored.

Ongoing clinical trials should further define the scope of the potential therapeutic role of VRAs.

Several clinical conditions are associated with abnormal water retention mediated by arginine vasopressin (AVP) release including heart failure, cirrhosis and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). A possible therapy targeting the AVP receptors in these disorders has been the subject of increasing interest.

This article reviews the current understanding of the role of vasopressin in these clinical conditions and the various types and functions of vasopressin receptors known to exist. The article then focuses on current vasopressin receptor antagonists (VRAs) also termed 'vaptans' and their potential therapeutic role.

1. Vasopressin

The structure of AVP or antidiuretic hormone was discovered ≈50 years ago, but its biological activities have been known for >100 years. It is a neuropeptide hormone produced in the supraoptic nuclei and paraventricular nuclei of the hypothalamus, and stored in the posterior pituitary.[1] It is also synthesised in peripheral tissues, including the heart, where it may act as a paracrine hormone.[2,3]

Normally, small changes in plasma osmolality, as little as 1%, influence the release of AVP by osmoreceptors in the hypothalamus, resulting in fine control of serum sodium levels and serum osmolality.[1] A decrease in blood volume also stimulates AVP release via baroreceptors, located in the carotid artery, aortic arch and left atrium, which sense changes in intra-arterial plasma volume.[1] In pathological states, including heart failure, non-osmotic mechanisms activated primarily by baroreceptors and including angiotensin II seem to play a greater role in the control of AVP release[4] (figure 1).

2. Arginine Vasopressin Receptors

AVP mediates significant cardiovascular and renal effects through at least three known receptor subtypes (V_{1A}, V_2 and V_{1B}) that belong to the seven transmembrane domain G- protein-coupled receptor

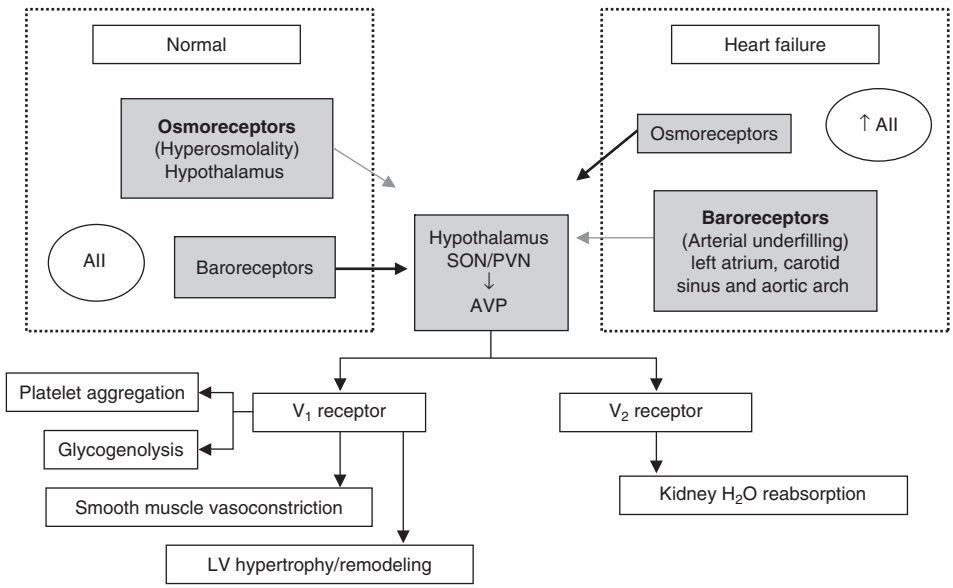

Fig. 1. Regulation of arginine vasopressin (AVP). Under normal circumstances AVP secretion is regulated by osmoreceptors in the hypothalamus with the baroreceptors playing a smaller role. In heart failure, despite reduced osmolality, arterial underfilling causes baroreceptors to have an overriding influence on AVP secretion. Angiotensin II (AII), elevated in heart failure, facilitates AVP release, which acts on its various receptors producing multiple effects. **LV** = left ventricular; **PVN** = paraventricular nuclei; **SON** = supraoptic nuclei; **V_1, V_2** = receptor subtypes; ↑ indicates increase.

Table I. Signalling, location and effects of vasopressin receptors

Receptor	Signalling	Location	Effects
V_{1A}	G-protein IP3, Ca^{2+}	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy
		Platelets	Platelet aggregation
		Hepatocytes	Glycogenolysis
		Myometrium	Uterine contraction
V_2	G-protein adenyl cyclase, cAMP	Basolateral membrane collecting tubule	Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis
		Vascular endothelium	vWF and factor VIII release
		Vascular smooth muscle	Vasodilatation
V_{1B}	G-protein IP3, Ca^{2+}	Anterior pituitary	ACTH release

ACTH = adrenocorticotropic hormone; **AQP2** = aquaporin-2; **cAMP** = cyclic adenosine monophosphate; **IP3** = phosphoinositol; **vWF** = von Willebrand factor.

superfamily.[5] They are identified by their second messenger systems, locations and effects (table I).

2.1 V_{1A} (or V_1) Receptors

The V_{1A} receptors are located on vascular smooth muscle cells, in the myocardium, hepatocytes and platelets, and when activated by AVP or agonists they mediate vasoconstriction in the coronary and peripheral circulation as well as glycogenolysis and platelet aggregation.[5] Increased intracellular calcium levels in cardiac myocytes and increased rate of protein synthesis have also been reported.[6,7] It is believed that myocyte hypertrophy is a direct result of these effects. *In vivo*, vasoconstriction is mitigated by decreased activity of the sympathetic nervous system as a result of central activation of the baroreflex system.[8] The receptors are linked to a phosphoinositol signalling pathway with intracellular calcium acting as a second messenger.

2.2 V_2 Receptors

The V_2 receptors are found predominantly in the collecting tubules of the kidney and mediate free water absorption by mobilising intracellular vesicles of aquaporin-2 to the apical plasma membrane of the collecting duct cells causing an increase in water permeability and an antidiuretic effect.[9] V_2 receptors are linked to an adenylate cyclase signalling pathway with intracellular cyclic adenosine monophosphate (cAMP) as a second messenger.[5,9]

However, V_2-mediated renal effects can be opposed by V_{1A} receptor-mediated generation of prostaglandin E_2 in the medullary interstitial cells, which explains the antidiuretic effect of NSAIDs.[5,10] Extrarenal V_2 receptors have also been implicated in von Willebrand factor secretion.[11]

2.3 V_{1B} (or V_3) Receptors

These receptors are found in the anterior pituitary and mediate adrenocorticotropic hormone release.[12] They have also been identified in peripheral tissues but their physiological role is yet to be determined.[12] The V_{1B} receptors, like the V_{1A} receptors, use a phosphoinositol signalling pathway with intracellular calcium as a second messenger.[12]

3. Role of Vasopressin in Disease States

Circulating levels of AVP have been found to be inappropriately elevated in several conditions including heart failure, SIADH, cirrhosis of the liver, polycystic kidney disease, nephrotic syndrome, surgical stress and some forms of hypertension.[1] It has been hypothesised that chronically elevated levels of AVP in heart failure might be involved in the pathophysiology as well as the progression of the disease state.[13,14] Higher levels are found in patients with more advanced disease and hyponatraemia.[14,15]

3.1 Hyponatraemia

Hyponatraemia is the most common electrolyte abnormality in hospitalised patients with a preva-

lence of 1–45% depending on the clincal setting, patient population and the serum value used to define it.[16-18] It is an established risk factor for increasing morbidity and mortality in patients with heart failure.[18,19] With the exception of renal failure, disorders that are associated with impaired renal water excretion are characterised by elevated AVP levels.[16] The most common cause for euvolaemic hyponatraemia is SIADH,[20] and for hypervolaemic hyponatraemia are heart failure[15] and cirrhosis.[21]

Current therapy for hyponatraemia include fluid restriction to <1 L/day, judicious infusion of hypertonic saline, diuretics, urea and demeclocycline. These measures are limited by low adherence, safety concerns and adverse effects.

Conivaptan, a V_{1A}/V_2 VRA, was approved by the US FDA in December 2005 and is the only FDA-approved vaptan for the treatment of euvolaemic hyponatraemia.

3.2 Heart Failure

Heart failure is commonly associated with hypervolaemic hyponatraemia. Hyponatraemia in heart failure correlates with both the severity and prognosis of the disease.[18,19] Hyponatraemia is multifactorial in heart failure, but is thought to be caused primarily by a low cardiac output state leading to a drop in renal blood flow and glomerular filtration rate, which reduces the rate of solute and water delivery to the distal diluting segment of the nephron. The low-output state causes the baroreflex system to sense a false volume-depleted state, resulting in release of AVP, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS).[22]

Binding of AVP to V_2 receptors in the collecting tubules results in stimulation of aquaporin-2 with subsequent increased free water reabsorption and decreased plasma osmolality.[8] The attempts of the osmotic receptors to suppress a rise in vasopressin levels is overridden by the baroreflex system and the cycle of worsening volume overload and hyponatraemia persists.[23] Moreover, activation of AVP V_{1A} receptors promotes vasoconstriction, increases afterload and potentially stimulates cardiac hypertrophy.[5,6]

In patients with heart failure, elevated AVP has been associated with increased mortality.[13,14] Progression of heart failure leading to signs and symptoms of congestion and worsening hyponatraemia seem to be related in part to neurohormonal activation and increased levels of renin, angiotensin, aldosterone, catecholamines and AVP. Large-scale clinical trials have shown reduction in mortality therapy with β-adrenergic antagonists (β-blockers), ACE inhibitors, angiotensin receptor antagonists (angiotensin receptor blockers; ARBs) and aldosterone antagonists.

Conventional therapy with loop diuretics and fluid restriction, however, has a limited effect on improving hyponatraemia. In addition, diuretics have undesirable side effects, including electrolyte depletion, and have been implicated in increasing mortality rate.[24-26] However, it should be kept in mind that because these analyses are retrospective, the worsened prognosis of heart failure patients taking diuretics could simply reflect selection bias of sicker patients.

Nevertheless, the potential increased mortality risk with diuretics coupled with the dilemma of correcting hyponatraemia in volume-overloaded patients stimulated exploration of a potential therapeutic role of vaptans in the pharmacological treatment of heart failure.

Blocking V_2 receptors is what is needed in order to induce diuresis with the advantage of not inducing kaliuresis. On theoretical grounds, combined blockade of V_{1A}/V_2 receptors may offer the advantage of inducing systemic vasodilation combined with removal of excess fluid. Furthermore, blockade of the V_{1A} receptors may prevent myocardial hypertrophy and remodelling based on *in vitro* studies[6-8] with no confirmation from *in vivo* studies to date.

3.3 Cirrhosis of the Liver

Cirrhosis, like heart failure, is characterised by hypervolaemic hyponatraemia, impaired delivery of solute to the diluting sites, impaired overall water excretion capacity and persistent inappropriate AVP

release by non-osmotic mechanisms. The similarity has brought attention to the role of AVP and potential therapeutic efficacy for AVP receptor blockade. However, the V_{1A} receptors in the setting of portal hypertension mediate AVP pressor effects, which when blocked may produce splanchnic vasodilatation that could promote variceal bleeding.[27] Therefore, at this time, only V_2 receptor antagonists are being explored in cirrhotic hyponatraemia.

3.4 Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH is characterised by inappropriately high AVP level despite hypotonicity.[28] Euvolaemic hyponatraemia ensues. Therapy in the past has targeted AVP secretion by agents such as ethanol, opiates and phenytoin (diphenylhydantoin), but with limited and unpredictable response. Decreasing the effects of AVP at target tissues is another approach that has had limited and often adverse effects.[5] Compensating for the effects produced by the excess hormone secretion, such as restricted fluid intake or hypertonic saline have been uncomfortable, difficult to adhere to, and often ineffective.[5] As stated in section 3.1, conivaptan was the first vaptan approved by the FDA for the treatment of euvolaemic hyponatraemia.

3.5 Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus may result from mutations to the V_2 receptor 2 gene (*AVPR2*) or aquaporin-2 (*AQP2*). There are three types of V_2 receptor mutations:[29] (i) type 1 mutations prevent AVP binding; (ii) type 2 mutations interfere with transport of the receptor from the endoplasmic reticulum to the cell membrane; and (iii) type 3 mutations involve unstable messenger RNA transcription. Interestingly, patients with congenital type 2 mutations in nephrogenic diabetes insipidus who were given relcovaptan had significantly increased urine osmolality.[30] These results suggest that V_{1A} and V_2 VRAs may improve transport of the receptor.[29,30] The future role of AVP antagonists in nephrogenic diabetes insipidus may be promising in certain types but needs further study.

3.6 Hypertension

Evolution may have implemented AVP as a part of the body's response to trauma or blood loss. Increased serum AVP levels in hypotensive states contributes to peripheral vasoconstriction, retention of water by kidneys, restoration of blood pressure and overall haemodynamic stabilisation.[31] In fact, vasopressin has been successfully tested for resuscitation and is recommended as an alternative to epinephrine (adrenaline) in current Advanced Cardiac Life Support Guidelines.[32,33]

While hypotension may increase AVP levels, measurement of plasma AVP in essential hypertension has not provided consistent results, with the exception of lack of correlation between blood pressure and AVP levels.[34] However, AVP appears to play an important role only after sympathetic inhibition.[34,35] In salt-dependent forms of experimental hypertension, elevated AVP levels appear to have a mediator role in the pathophysiology of at least the initiation of elevated blood pressure.[34] For example, studies with mineralcorticoid-induced hypertension in rats indicate that AVP plays a significant pathophysiological role.[36]

Ethnicity has been suggested to influence the role of AVP in hypertension. In elderly hypertensive patients, increased AVP level has been noted in African Americans compared with an age-matched hypertensive Caucasian group.[37] In one study of 39 hypertensive patients, treatment with a V_{1A} antagonist lowered blood pressure in African Americans but not Caucasians before and after treatment with clonidine.[38]

It is proposed that antagonism of both V_{1A} and V_2 receptors may play a role in the treatment of hypertension by a combination of lowering vascular resistance and circulating volume, but there is still much investigation left in this area.

3.7 Polycystic Kidney Disease

In this disorder, cAMP-dependent genes increase cell proliferation and promote fluid-filled renal cysts.[39] As mentioned previously, the V_2 receptor uses cAMP as a second messenger. Studies in animal models have led to the theory that a V_2 VRA

may reduce cAMP levels, thus interfering with the genes responsible for promoting polycystic kidney disease.[40]

4. Vasopressin Receptor Antagonists (VRAs)

AVP receptor antagonists were first developed as peptide antagonists in the 1960s. Although these peptides mediated antagonism to both antidiuretic and pressor responses in animals, a paradoxical weak agonism to the V_2 receptor was seen in human studies.[5] This was believed to be due to species differentiation of prostaglandins in the kidney. Also disappointing was the fact that these compounds had poor oral bioavailability and short biological half-lives.[5]

Employing a functional screening strategy, the first non-peptide V_2 antagonist was characterised in 1992 in Japan by Yamamura et al.[41] These non-peptide VRAs appeared to be more bioavailable with longer half lives than the earlier peptide formulations. Several non-peptide VRAs have been studied in human clinical trials. These vaptans include conivaptan, tolvaptan, lixivaptan, relcovaptan (SR-49059) and satavaptan (SR-121463), which were developed as oral or intravenous formulations and were all derived from benzazepine or oxindole derivatives (table II). They differ in their relative selectivity for the various AVP receptor subtypes (table III).

4.1 V_{1A} VRA

Acute V_{1A} receptor antagonism has been shown to be synergistically beneficial when combined with angiotensin II antagonism in improving myocyte function and cardiac load in a pacing-induced heart failure model.[43] Interestingly, V_{1A} VRAs have been shown to be more potent in models with absent RAAS and adrenergic systems.[44-46]

Preliminary work with relcovaptan (SR-49059) suggested that it might be haemodynamically beneficial in heart failure patients with elevated plasma AVP levels and hypertensive patients with low plasma AVP levels.[35,47] This has led to the postulation that AVP plasma levels may not predict haemodynamic effects. Limited data are available in long-term administration of V_{1A}-receptor antagonists.

The expected haemodynamic effects of chronic V_{1A}-receptor antagonism such as arterial vasodilation, decreased afterload, and possibly reduction of direct myocyte stimulation and hypertrophy have shown promise in animal models but, disappointingly, V_{1A}-receptor antagonists turned out as partial agonists in human models.[48]

4.2 V_2 VRA

The V_2 VRAs have had more promising results than the V_{1A} VRAs. Blocking V_2 receptors in the distal collecting tubule of the kidney causes an aquaresis, which is an electrolyte-sparing water excretion, which is different from diuresis. In experimental studies, there also appears to be less activation of the RAAS and adrenergic sympathetic system when compared with furosemide.[49]

4.2.1 Tolvaptan

Tolvaptan is an oral, selective V_2 VRA that has shown to be a potent aquaretic in both animal and human studies. In a double-blind, placebo controlled trial, 254 patients with systolic heart failure were randomised to tolvaptan 30, 45, 60mg or placebo for 25 days.[50] The primary endpoint was change in bodyweight from baseline. Patients were maintained

Table II. Non-peptide vasopressin antagonists currently under commercial development (reproduced from Greenberg and Verbalis,[27] with permission from Macmillan Publishers Ltd [Kidney International] © 1999)

Compound	Receptor	Route	Manufacturer
Conivaptan[a] (YM-087)	V_{1A} + V_2	Intravenous	Astellas (Tokyo, Japan)
Lixivaptan (VPA-985)	V_2	Oral	CardioKine (Philadelphia, PA, USA)
Tolvaptan (OPC-1061)	V_2	Oral	Otsuka (Tokyo, Japan)
Satavaptan (SR-121463)	V_2	Oral	Sanofi-Aventis (Paris, France)

a Approved for euvolaemic hyponatraemia.

Table III. Comparison of arginine vasopressin antagonists (reproduced from Lee et al.,[42] with permission from Elsevier)

	Tolvaptan	Lixivaptan	Satavaptan	Conivaptan
Receptor	V_2	V_2	V_2	V_{1A}/V_2
Selectivity (KiV_1 : KiV_2)	29 : 1	100 : 1		10 : 1
Route	Oral	Oral	Oral	Intravenous
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Sodium excretion/24h	↔	↔ At low doses ↑ At high doses	↔	↔

Ki = dissociation constant of the inhibitor; ↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.

on heart failure medications without fluid restriction. A total of 221 patients (87%) completed the study. All three doses of tolvaptan were associated with significant reduction in bodyweight 24 hours after administration (−0.79 ± 0.99, −0.96 ± 0.93, −0.84 ± 0.02 and +0.32 ± 0.46kg in the 30, 40, 60mg and placebo groups, respectively; $p < 0.001$) with significant increases in urine output (3.9 ± 0.6, 4.2 ± 0.9, 4.6 ± 0.4 and 2.3 ± 0.2L per 24 hours for the 30, 45, 60mg and placebo groups, respectively; $p < 0.0001$). The tolvaptan-treated groups had small increases in mean serum sodium, whereas the placebo group became slightly more hyponatraemic (figure 2).

Reduction in oedema was also observed in the tolvaptan-treated groups. No significant changes were seen in heart rate, blood pressure, serum potassium or renal function in any of the treatment groups. The adverse effects seen more commonly in the treatment groups than placebo included thirst, dry mouth and polyuria.[50]

In the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) trial, 319 hospitalised patients with heart failure exacerbation were randomised to tolvaptan 30, 60, 90 mg/day or placebo for up to 60 days in addition to standard heart failure therapy.[51] The first primary endpoint was change in bodyweight 24 hours after receiving the first dose of tolvaptan. After 1 day, median bodyweight (range) changed by −1.8 (−3.85 to −0.50), −2.10 (−3.10 to −0.85), −2.05 (−2.80 to −0.60) and −0.60kg (−1.60 to 0.00) in the 30, 60 and 90mg tolvaptan and placebo groups, respectively ($p \leq 0.0008$ for all treatment groups vs placebo). There was a significant increase in urine output in the first 24 hours, which was maintained throughout the hospital period. There were no significant changes in serum potassium or renal function. Sodium normalisation was higher in the treatment groups and sodium correction in the treatment period was maintained throughout the study. There was no significant difference in the second primary endpoint (death, hospitalisation or unscheduled visit for heart failure) at 60 days. A *post hoc* analysis showed lower total mortality with tolvaptan in patients with elevated blood urea nitrogen levels (>29 mg/dL), and severe systemic congestion defined as presence of oedema, jugular venous distention and dyspnoea.[51]

The VICTOR (Vasopressin Inhibition in CHF by Tolvaptan Oral Regimen) study involved 83 patients with New York Heart Association (NYHA) II–III

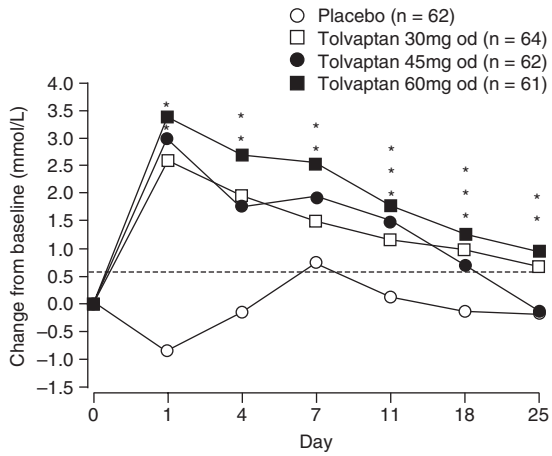

Fig. 2. Effect of tolvaptan on serum sodium in patients with congestive heart failure. * $p < 0.05$ vs placebo (reproduced from Gheorghiade et al.,[50] with permission from Lippincott, Williams & Wilkins). **od** = once daily.

heart failure who were placed on a low-sodium diet and were taken off baseline diuretics for 2 days at which time they were randomised to placebo, monotherapy with tolvaptan 30mg, furosemide 80mg or both once daily. At 1 week, tolvaptan monotherapy reduced bodyweight and oedema compared with placebo without significant changes in electrolytes. Compared with furosemide, an increase in urine output but no change in bodyweight was noted with both tolvaptan and tolvaptan plus furosemide.[52]

The METEOR (Multicenter Evaluation of Tolvaptan Effect On Remodeling) study assessed the effects of tolvaptan on left ventricular size and function. A total of 240 patients with symptomatic heart failure (NYHA II and III), left ventricular ejection fraction <30% were randomised to tolvaptan 30 mg/day or placebo. After 1 year of therapy, there were no differences in left ventricular volume or ejection fraction.[53]

The ongoing double-blind, placebo-controlled trial, EVEREST (Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan), is expected to reveal much anticipated information on mortality, morbidity and patient-assessed global clinical status in tolvaptan-treated patients compared with standard care.[54]

4.2.2 Lixivaptan

Lixivaptan is an orally active selective V_2 VRA that has shown potent aquaresis in animals and humans.[55] In a recently published double-blind, placebo-controlled, single-dose study, 42 patients with heart failure were randomised to lixivaptan 10, 30, 75, 150, 250 or 400mg after overnight fluid deprivation.[56] Lixivaptan produced significant dose-related increase in urine volume and solute-free water excretion at all doses except the 10mg dose. Higher serum osmolality and serum sodium levels were noted at the 75mg or higher and the 150mg or higher doses, respectively. The drug was well tolerated.

In a randomised, placebo-controlled study, 44 hospitalised patients with stable hyponatraemia mostly from cirrhosis were randomised for 7 days to lixivaptan 25, 125, 250mg or placebo twice daily. A significant improvement in aquaresis ($p < 0.05$) was noted in the two highest doses without significant alteration in haemodynamics, electrolytes or renal function.[57] There was significant increase in serum sodium levels and osmolality. Fifty percent of patients taking the 250mg dose (n = 5) had the dose held several times because of significant dehydration as determined by thirst score, and marked increases in serum sodium levels. By day 7, there were marked increases in AVP levels in the two highest dose lixivaptan groups, which may have accounted for the plateauing of the aquaretic effect with repeated administration.[57]

In another double-blind, placebo-controlled study, 60 patients with hyponatraemia and cirrhosis were randomised to lixivaptan 100 or 200mg or placebo for 7 days or until serum sodium levels increased to >136 mmol/L.[58] Patients were fluid restricted to 1 L/day. Serum sodium levels normalised in 0%, 27% and 50% in the placebo, 100mg ($p < 0.05$) and 200mg ($p < 0.0001$) groups, respectively. Significant reduction in urine osmolality and bodyweight were also seen in the treated group. A marked increase in thirst was seen in the 200mg group but not the 100mg group. Serious adverse effects like renal insufficiency were seen equally in all three groups.[58]

Although promising, more studies are needed to assess the future of lixivaptan in clinical practice.

4.2.3 Satavaptan

Satavaptan is an orally active selective V_2 VRA that has been shown in a randomised, double-blind, placebo-controlled study in 37 patients with hyponatraemia due to SIADH to be effective in the treatment of hyponatraemia.[59] Two dosages of satavaptan were evaluated, 25 and 50mg. Normalisation of serum sodium levels or an increase by ≥5 mEq/L were noted in 13% of patients receiving placebo compared with 79% of patients receiving satavaptan 25mg ($p = 0.006$) and 83% of patients receiving satavaptan 50mg ($p = 0.005$). No significant serious adverse events were noted.

Although the published experience with satavaptan is limited, the preliminary results are encouraging.

4.3 V_{1A}/V_2 VRA

4.3.1 Conivaptan

Conivaptan is a non-peptide V_{1A}/V_2 VRA that has been shown in animal studies to induce significant aquaresis, marked haemodynamic improvements and reduced myocyte protein synthesis.[60-62]

Conivaptan is the only FDA approved vaptan at this time for use in euvolaemic hyponatraemic patients as an intravenous infusion. Development of the oral formulation was discontinued because of potent inhibition of the CYP3A4 isoenzyme in the liver and small intestine, and significant drug-drug interactions.

In an intravenous randomised, placebo-controlled, double-blind trial, 66 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium levels between 115–130 mEq/L)[63] following 24-hour baseline placebo infusion received an intravenous loading dose of conivaptan 20mg or placebo, followed by continuous infusion of conivaptan 40, 80mg or placebo for 4 days. A significant increase in serum sodium levels (the primary endpoint) was seen with conivaptan 40 and 80 mg/day.[63]

In a 5-day placebo-controlled, randomised, double-blind study involving 74 in-patients with hyponatraemia, oral conivaptan 40 and 20 mg/day was well tolerated and efficacious in correcting serum sodium levels[64] (figure 3).

While the FDA approved use is currently for euvolaemic hyponatraemia, the theoretical benefit of aquaresis from V_2-receptor antagonism in addition to the beneficial haemodynamic changes due to the V_{1A} receptor antagonism make this antagonist attractive for conditions characterised by hypervolaemic hyponatraemia such as heart failure.

The double-blind, placebo controlled study, ADVANCE (A Dose evaluation of a Vasopressin An-

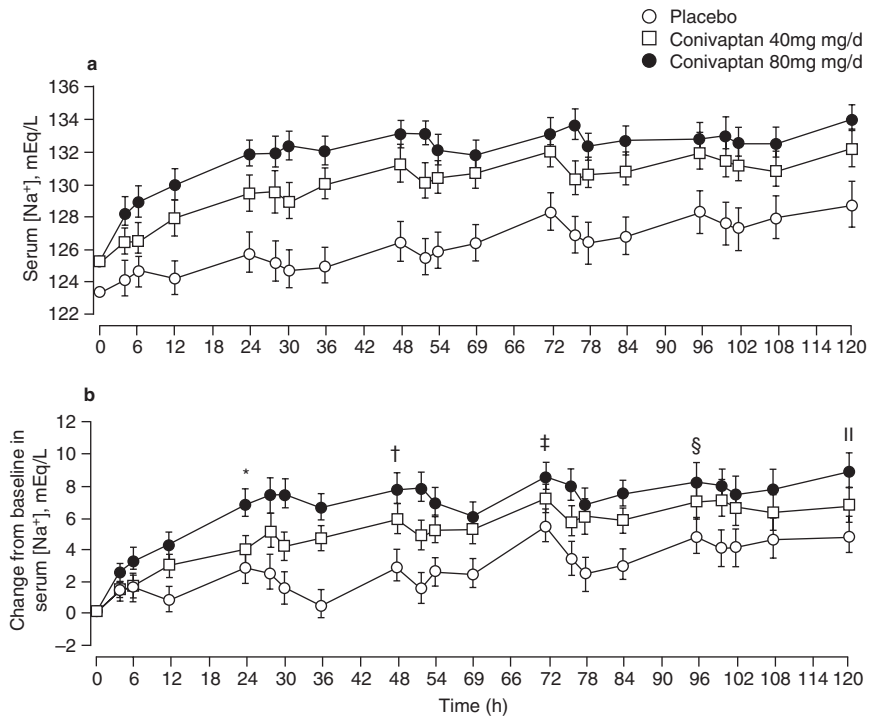

Fig. 3. Results of a 5-day placebo-controlled, randomised, double-blind study of conivaptan in patients with hyponatreamia. Mean ± standard error (SE) serum [Na+] (**a**) and least squares mean ± SE change from baseline in serum [Na+] (**b**) at baseline (0h) and at each measurement time, by treatment group. * $p < 0.002$; † $p < 0.001$; ‡ $p = 0.029$; § $p = 0.037$; II $p = 0.018$ (vs placebo) [reproduced from Ghali et al.,[64] with permission. Copyright © 2006, The Endocrine Society].

tagonist in CHF patients undergoing Exercise), evaluated the effect of 12-week administration of conivaptan (10, 20 or 40mg daily) on symptoms and functional capacity in 343 patients with heart failure.[65] There were no statistically significant differences between the treated and placebo groups in exercise duration or symptoms.[65]

In a haemodynamic, double-blind study, 142 patients NYHA class III–IV were randomised to a single intravenous dose of conivaptan (10, 20 or 40mg) or placebo.[66] In the higher dose conivaptan groups, pulmonary capillary wedge and right atrial pressures were significantly reduced compared with placebo at 3 and 6 hours after administration. There was also a significant dose-dependent increase in urine output during the first 4 hours after administration. No differences in cardiac index, systemic or pulmonary vascular resistance, blood pressure or heart rate were noted, leading to the postulation that the haemodynamic changes were related more to the volume loss secondary to the V_2-receptor antagonism.[66]

In a combined analysis of three trials, one with intravenous and two with oral administration, conivaptan 40 and 80 mg/day significantly increased serum sodium levels in hyponatraemic patients with (n = 94) and without (n = 147) heart failure.[67]

However, it should be emphasised that initial FDA approval for conivaptan was restricted to the intravenous formulation of conivaptan for the treatment of euvolaemic hyponatraemia.

5. Conclusions

Recognition of the important role that AVP plays in circulatory and sodium homeostasis has led to identification of several receptor subtypes that mediate its actions and the development of non-peptide antagonists to these receptors. Antagonism of V_{1A} receptors located in vascular smooth muscle cells results in vasodilation and antagonism of V_2 receptors located in the renal collecting duct results in aquaresis. Extensive clinical testing is underway to define the therapeutic potential of VRAs. Conivaptan, a combined V_{1A}/V_2-receptor antagonist, has been approved for the intravenous treatment of euvolaemic hyponatraemia. Tolvaptan, a selective V_2-receptor antagonist, is being evaluated for the treatment of hyponatraemia and heart failure, including its effect on heart failure morbidity, mortality and quality of life.

A very promising therapeutic potential of VRAs in addition to hyponatraemia includes conditions characterised by fluid overload, such as heart failure and cirrhosis. Furthermore, attenuating polyuria in nephrogenic diabetes insipidus and cyst development in polycystic kidney disease are exciting areas for potential future use for these agents.

Clinical experience and future clinical trials should continue to define the scope and proper therapeutic role of the various VRAs.

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Correspondence: Dr *Jalal K. Ghali*, University Health Center, 4201 St Antoine, Detroit, 2E, MI 48201, USA.
E-mail: jghali@med.wayne.edu