

# Conivaptan and its role in the treatment of hyponatremia

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**Abstract:** Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is associated with increased morbidity and mortality. The recognition of the central role that arginine vasopressin plays in the pathogenesis of hyponatremia and the discovery that its actions are mediated by stimulation of  $V_{1A}$  and  $V_2$  receptors have led to the development of a new class of drugs, the arginine vasopressin antagonists. Conivaptan is a nonselective  $V_{1A}$  and  $V_2$  receptors antagonist that was the first of this class to be approved by the FDA for the management of euvoletic and hypervolemic hyponatremia. Its short-term safety and efficacy for the correction of hyponatremia have been established by multiple double-blind, randomized, controlled studies. Blocking the effects of arginine vasopressin on  $V_2$  receptors produces aquaresis – the electrolyte-sparing excretion of water – an ideal approach to correct hypervolemic hyponatremia. The nonselectivity of conivaptan offers a theoretical advantage for its use in heart failure that may merit further exploration.

**Keywords:** arginine vasopressin antagonist, conivaptan, heart failure, hyponatremia

## Introduction

Hyponatremia is the most common electrolyte abnormality seen in hospitalized patients. Although recognized for almost a century, our understanding of hyponatremia remains incomplete and its management continues to represent a challenge. The presence of inappropriately elevated plasma level of arginine vasopressin (AVP) is well established in the vast majority of hyponatremic states, and the development of arginine vasopressin antagonists signaled the beginning of a new treatment option for hyponatremia. Conivaptan was the first such agent to be approved for this indication in euvoletic and hypervolemic states.

This article reviews the pathogenesis of hyponatremia and the pathophysiological basis for the development of conivaptan, its properties, the experience accumulated from clinical trials, and its current use and potential future role.

## Prevalence

The prevalence of hyponatremia varies depending on the definition used, patient population, and the frequency of testing.<sup>1</sup> When defined as  $\leq 135$  milliequivalent per liter (mEq/L or mmol/L), the prevalence was reported in 40,000 hospitalized patients at 28% on admission, with the development of hyponatremia in another 14% while in the hospital.<sup>2</sup> However, figures as low as 5.5% have also been reported.<sup>3</sup>

In patients with heart failure, using this definition, a prevalence of 20% to 45% has been reported in several large registries.<sup>4-8</sup> The prevalence would be considerably higher,

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however, if a cutoff of 138 mEq/L were adopted to define hyponatremia,<sup>9</sup> a level below which an increased morbidity and mortality was noted in this patient population.<sup>8</sup>

## Clinical manifestations

The clinical manifestations of hyponatremia are related to osmotic water shift leading to increased intracellular fluid volume causing cerebral edema. Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops and may cause brain injury.<sup>10–13</sup> Therefore, symptoms are primarily neurologic and their severity depend on the rapidity of development of hyponatremia and its magnitude.<sup>10–13</sup> Patients may be asymptomatic or they may develop symptoms such as malaise, headache, nausea, vomiting, lethargy, depressed reflexes and confusion. As the plasma  $[Na^+]$  falls below 120 mEq/L and especially if the disorder has developed rapidly, stupor, seizures, brain stem herniation and coma may occur.<sup>10–13</sup> Solutes leave the brain tissue within hours, thereby inducing water loss and reducing brain swelling.<sup>13</sup> This adaptive mechanism accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly.<sup>10–14</sup>

## Pathophysiology

Hyponatremia is defined as a decreased serum  $[Na^+]$  concentration (traditionally  $\leq 135$  mEq/L). Accordingly, hyponatremia reflects a disturbance in water rather than  $[Na^+]$  balance, although several interactions between the two regulatory systems exist. The definition of hyponatremia is based on concentration; therefore it does not provide information on extracellular fluid volume (ECF) in which  $[Na^+]$  is measured. As a result, hyponatremia can occur in the context of contracted ECF (hypovolemia), normal ECF (euovolemia) or expanded ECF (hypervolemia).<sup>10</sup>

Many conditions can lead to hyponatremia, which can be associated with low, normal or high osmolality.<sup>14</sup> Hypo-osmolar hyponatremia is by far the most common form of this disorder,<sup>10</sup> and is caused by multiple medical conditions (Table 1). Hyponatremia can be associated with normal plasma osmolality in cases of extreme hyperlipidemia or hyperproteinemia (pseudohyponatremia) or high osmolality in hyperglycemia and with mannitol use, secondary to a shift of water from the cells to the extracellular compartment.<sup>10,15,16</sup>

## Arginine vasopressin

Water balance regulation is primarily designed to control serum osmolality and to a lesser extent blood volume,<sup>17</sup> and the

**Table 1** Causes of hyponatremia

I. Hyponatremia with normal plasma osmolality (pseudohyponatremia)
1. Hyperlipidemia
2. Hyperproteinemia
II. Hyponatremia with increased plasma osmolality
1. Hyperglycemia
2. Mannitol use
3. Radiographic contrast agents
III. Hypo-osmolar (hypotonic) hyponatremia
A. Euvolemic
1. Syndrome of inappropriate antidiuretic hormone secretion
2. Hypothyroidism
3. Glucocorticoid deficiency
4. Strenuous exercise
5. Primary polydipsia
6. Decreased solute intake
B. Hypervolemic
1. Heart failure
2. Cirrhosis
3. Nephrotic syndrome
4. Pregnancy

central role of AVP in the pathogenesis of hyponatremia was recognized more than half a century ago.<sup>18,19</sup>

AVP is synthesized primarily in the magnocellular neurons of the hypothalamic paraventricular nuclei and in the supraoptic nuclei that project to the posterior pituitary.<sup>20</sup> In addition, parvocellular neurons of the paraventricular nuclei co-expressing AVP and corticotropin-releasing hormone (CRH) coordinate hypothalamic–pituitary–adrenal (HPA) system activity and project to the external layer of the median eminence, where AVP and CRH are released into the hypophyseal portal blood.<sup>21</sup> The AVP precursor protein contains sequences for 3 separate peptides which split during transport down the nerve axon to the posterior pituitary into AVP, neurophysin and a glycopeptide.

AVP is regulated by 3 mechanisms: osmoreceptors, baroreceptors and the rennin-angiotensin aldosterone system (RAAS).

Under normal conditions, the release of AVP is primarily controlled by the osmoreceptors.<sup>22</sup> The serum osmolality is sensed by osmoreceptors in several parts of the brain, including the supraoptic nuclei of the hypothalamus, the subfornical organ, and the organum vasculosum of the lamina terminalis.<sup>22,23</sup> Osmolality is regulated by thirst and renal responsiveness to AVP in addition to AVP release.<sup>23</sup> Alterations of the plasma osmolality are detected by

the osmoreceptors in the vicinity of the supraoptic and paraventricular areas of the anterior hypothalamus, which are supplied by blood from the internal carotid. A rise in serum osmolality causes water to move through the water channels of the osmoreceptor cell membranes, which then causes a change in cell volume that leads to an increase in the activity of stretch-inhibited cation channels.<sup>21</sup> The accelerated action potential discharge causes an influx of calcium through a voltage-gated calcium channel which triggers a cascade of molecular events that ultimately leads to the neurosecretion of secretory vesicles containing AVP into the bloodstream.<sup>21,22</sup>

AVP starts to rise after 1% increase in serum osmolality or 5% to 10% decrease in blood volume.<sup>17</sup> The second mechanism regulating AVP release is mediated by baroreceptors located in the carotid sinus and stretch receptors in the walls of the great veins, atria and pulmonary trunk. These receptors are sensitive to changes in circulating blood volume triggered by hypotension and/or volume depletion. In conditions characterized by arterial underfilling such as low cardiac output or decreased systemic vascular resistance the baroreceptors generate afferent signals to the vasomotor center. This results in activation of efferent pathways in the sympathetic nervous system (SNS) leading to increase in the rate of AVP secretion by the cells in the paraventricular and supraoptic nuclei.<sup>24</sup>

The third mechanism is related to actions of the RAAS,<sup>25,26</sup> in which angiotensin II directly stimulates the secretion of AVP.

In the majority of patients, hyponatremia develops because AVP is secreted nonosmotically, resulting in renal water reabsorption. The four mechanisms that can cause inappropriate AVP effects<sup>27</sup> include: (1) nonosmotic AVP release by the posterior pituitary induced by specific stimuli to the paraventricular or supraoptic nuclei;<sup>24</sup> (2) ectopic AVP production;<sup>28</sup> (3) factors that may enhance the renal effects of AVP;<sup>29</sup> and (4) an AVP-like effect caused by an activating mutation of the vasopressin-2 receptor.<sup>27,30</sup>

The neurohypophysial antidiuretic hormone AVP regulates free water reabsorption, body fluid osmolality, blood volume, blood pressure, cell contraction, cell proliferation and adrenocorticotrophic hormone (ACTH) secretion via the stimulation of specific G-protein-coupled receptors currently classified into  $V_1$ -vascular receptor ( $V_{1A}$ ),  $V_2$ -renal receptor ( $V_2$ ) and  $V_3$ -pituitary receptor ( $V_{1B}$ ) subtypes.<sup>31,32</sup>

## Vasopressin receptors

The  $V_{1A}$  receptors are found mainly on vascular smooth muscle cells but also in many tissues, including brain, pituitary,

hepatic, uterus, renal, adrenal, and platelets,<sup>31,32</sup> while the  $V_{1B}$ , distinguished from the  $V_{1A}$  subtype by different agonist and antagonist affinities, are expressed in cells of the anterior pituitary and throughout the brain, especially in the pyramidal neurons of the hippocampus and in the pancreas.<sup>33,34</sup> The renal receptors ( $V_2$ ) are located on the principal cells of the collecting ducts of kidney and in vascular smooth muscle and endothelial cells.<sup>31,32</sup>

Stimulation of the  $V_{1A}$  receptor results in vasoconstriction, glycogenolysis, platelet aggregation, myocyte hypertrophy, anxiety and stress.<sup>31,32</sup> While stimulation of the  $V_{1B}$  receptor results in the release of ACTH.<sup>35,36</sup>

Stimulation of the  $V_2$  receptor results in vasodilatation, release of von Willebrand factor and factor 8 as well as water retention.<sup>31,35</sup> The effect of AVP on vascular contractility is dose-dependent. At low concentrations, it causes vasoconstriction and, at higher concentrations, it causes vasodilatation.<sup>37</sup>

AVP exerts its actions through binding to typical heptahelical transmembrane G-protein-coupled receptors with distinct second messenger systems; stimulation of the  $V_{1A}$  and  $V_{1B}$  receptors ultimately results in a considerable increase in the cytosolic free calcium as a secondary messenger via phosphatidylinositol hydrolysis and 1,2 diacylglycerol signaling pathway. The calcium signal may express its activity through a number of binding proteins including calmodulin, gelsolin or villin, troponin C or protein kinase C.<sup>28</sup>

Stimulation of the  $V_2$  receptor on the other hand leads to the activation of adenylyl cyclase, resulting in an increase of intracellular c-AMP, and protein kinase A (PKA), which triggers phosphorylation of many proteins including aquaporin 2 (AQP-2).<sup>31</sup> c-AMP then causes fusion of AQP-2 containing intracytoplasmic vesicles with the apical plasma membrane of the principal cell, leading to increased permeability and thus enhanced water reabsorption.<sup>28,31,37</sup>

The presence of AQPs in combination with an osmotic gradient allows water to move through the baso-lateral plasma membrane of the principal cell, returning to the bloodstream via the constitutively expressed AQP3 and AQP4 water channels.<sup>29,38</sup> AVP also increases  $[Na^+]$  and urea permeability in the collecting duct (by increasing the number of the epithelial  $[Na^+]$  channel, ENaC, and the urea transporter, UT-A1), thereby maintaining the osmotic and medullary interstitial gradients and further stimulating antidiuresis.<sup>38</sup>

## Vasopressin receptors antagonists (VRAs)

AVP receptors antagonists were first developed as peptide antagonists in the 1960s. These compounds had the

disadvantages of having poor oral bioavailability and short half-lives.<sup>39</sup> The first nonpeptide  $V_2$  antagonist was characterized in Japan by Yamamura et al in 1991.<sup>40</sup> The nonpeptide VRAs were more bioavailable, with longer half-lives, than the earlier peptide formulations.<sup>39</sup>

Several nonpeptide VRAs have been studied, and were developed as oral or intravenous (iv) formulations. They differ in their relative selectivity for the various AVP receptor subtypes<sup>31</sup> and include tolvaptan (oral, selective  $V_2$  VRA) that was recently approved by the United States Food and Drug Administration (FDA) for the treatment of symptomatic or severe hyponatremia (serum  $[Na^+] < 125$  mEq/L); lixivaptan (oral, selective  $V_2$  VRA) which is currently under intense investigation for its potential role in the treatment of hyponatremia in heart failure; and conivaptan, the first approved nonpeptide  $V_{1A}/V_2$  VRA that will be discussed in more details.

It would be useful, however, to first briefly review the reasons for the search for more effective modality for the treatment of hyponatremia.

## Limitations of current treatments for hyponatremia

There are many limitations to the use of traditional treatment of hyponatremia.<sup>41,42</sup> The infusion of hypertonic saline, increasing serum  $[Na^+]$  by 2 to 4 mEq/L within 2 to 4 hours is associated with significant fluid overload and many clinicians are uncomfortable using it in patients with volume overload. Fluid restriction plays a cornerstone role in the treatment of hyponatremia but it is fraught with problem of compliance. Lithium has also been used to induce nephrogenic diabetes insipidus, but it has many side effects including renal impairment, central nervous system effects and thyroid dysfunction. The response is erratic and frequent monitoring is needed to ensure that blood levels remain within the therapeutic range. Demeclocycline is another treatment option, but it has many drawbacks including variable response to treatment, poor gastrointestinal tolerance, photosensitivity and renal and hepatic toxic effects. Urea has been used in patients with severe symptoms as it promotes rapid reduction of brain edema without the risk of salt overload that accompany hypertonic saline, however, it is not well tolerated due to poor palatability and the need for concomitant fluid restriction to achieve good results. Finally, diuretics often do not correct hypotonic hyponatremia, they may actually contribute to hyponatremia by promoting excretion of  $[Na^+]$  and decreasing the excretion of electrolyte-free water. In addition, the effectiveness of diuretics is related to the amount of  $[Na^+]$

reaching the loop of Henle and diminished  $[Na^+]$  delivery in advanced heart failure results in diminished diuresis.

## Conivaptan (YM087)

Conivaptan hydrochloride is a nonpeptide, benzazepine derivative and the only dual  $V_{1A}$  and  $V_2$  AVP receptor antagonist. It has almost no effect on  $V_{1B}$  receptors. *In vitro* animal studies have shown that the drug has high affinity for both  $V_{1A}$  and  $V_2$ .<sup>44</sup> The antagonistic effect of conivaptan is concentration dependent and it binds competitively with an affinity 10-fold higher for  $V_2$  than for  $V_{1A}$  receptors<sup>45</sup> and binds reversibly to both receptors.

Conivaptan was discovered first in Japan by Yamanouchi Pharmaceutical Co. Ltd., and further developed in the United States, by Astellas Pharma US Inc.<sup>43</sup>

It is the first AVP receptors antagonist to be approved by FDA for the use in the management of refractory euvolemic and hypervolemic hyponatremia, as intravenous infusion in the inpatient setting.

## Pharmacokinetics

The pharmacokinetics of conivaptan has been studied using both oral and iv formulations in animals and humans (Table 2). In a study in the rat, oral formulation effect was dose dependant and persisted for more than 24 hours showing possibilities of long duration of action.<sup>44,45</sup> In humans, oral conivaptan, at a dose of 60 mg, showed 44% bioavailability and short half-life in 6 healthy individuals, and its pharmacodynamic effects persisted for at least 6 hours.<sup>46</sup>

In a study among healthy male subjects, conivaptan was administered as 20 mg loading dose (infused over 30 minutes) followed by continuous infusion of 40 mg/day for 3 days. Mean  $C_{max}$  for conivaptan was 619 ng/mL and occurred at the end of the loading dose, plasma concentration reached a minimum at approximately 12 hours after the start of the loading dose, and then gradually increased over the duration of the infusion to a mean concentration of 188 ng/mL at the end of the infusion. The mean terminal elimination half-life after conivaptan infusion was 5.0 hours, and the mean clearance was 15.2 L/hour.<sup>47</sup>

## Drug formulation and dosing

Conivaptan hydrochloride is a white to off-white or pale orange-white powder that is very slightly soluble in water (0.15 mg/mL at 23 °C). Conivaptan injection is supplied as a sterile liquid in an ampule. Each ampule delivers 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g ethanol, and water for injection. Lactic acid is added

**Table 2** Pharmacokinetics of conivaptan

Parameter	Drug
$C_{max}$ (at 0.5 h)	619 ng/mL – median, healthy males (20 mg loading dose/20 mg/day) 575.8 (144.5 to 764.3) ng/mL – median, hyponatremic patients (20 mg loading dose/20 mg/day) 781.1 (194.5 to 1373.5) ng/mL – median, hyponatremic patients (20 mg loading dose/40 mg/day)
$T_{max}$	30 min (end of iv loading dose)
$V_d$	32L
$t_{1/2}$	Variable (secondary to nonlinear kinetics)
Protein binding	99%
Metabolism	CYP3A4 (substrate and potent inhibitor); 4 active metabolites identified with minimal clinical effect
Elimination	Eliminated primarily as metabolites (<1% recovered intact drug in urine) 83% feces 12% urine
Mean clearance	15.2 L/h
Bioavailability	44% absorption with oral conivaptan formulation

for pH adjustment to 3.0.<sup>47</sup> A loading dose of 20 mg is administered through a large vein given over 30 min followed by a maintenance dose of 20 to 40 mg/day for up to 4 days by continuous infusion. It is recommended to change the infusion site every 24 hours to avoid infusion site complications. Close monitoring of serum  $[Na^+]$  and volume status is recommended so the dose can be adjusted accordingly.

## Metabolism

Conivaptan is 99% bound to human plasma protein at concentration range of 10 to 1000 ng/mL. It is metabolized only by the liver cytochrome P450 isozyme (CYP3A4). The pharmacokinetics of oral and iv conivaptan are nonlinear. Four metabolites have been identified, and inhibition by conivaptan of its own metabolism seems to be the major factor for the nonlinearity.<sup>47</sup> The pharmacological activity of the metabolites at  $V_{1A}$  and  $V_2$  receptors ranged from approximately 3% to 50% and 50% to 100% that of conivaptan, respectively. After 10 mg iv or 20 mg oral dose, approximately 83% is excreted in feces, and 12% in urine. Approximately 1% of the iv dose is excreted as intact conivaptan in urine within 24 hours.<sup>47</sup> Studies in special populations, including patients with renal and hepatic insufficiency, demonstrated higher levels of conivaptan after oral intake. Since iv conivaptan results in higher exposure to the drug, caution should be used in patients with hepatic or renal impairment.<sup>47</sup>

## Drug interaction

Conivaptan is a sensitive substrate as well as a potent inhibitor of CYP3A4.<sup>43</sup> Concomitant use of conivaptan with other drugs metabolized by CYP3A4 could result in a significant drug interaction, either by an increase in conivaptan levels, or an increase other drug levels and

potentially their side effects.<sup>43</sup> By decreasing clearance via CYP3A4, conivaptan can increase the risk of toxicity of certain drugs such as midazolam, simvastatin and amlodipine. For example, 30 mg/day of iv conivaptan resulted in a 3-fold increase in the area under the curve (AUC) of simvastatin and was associated with an increased incidence of rhabdomyolysis.<sup>47</sup> It also decreased the systemic clearance of digoxin by approximately 30% and thus increased its AUC and  $C_{max}$  values potentiating digoxin toxicity. The pharmacokinetics of conivaptan was unchanged with co-administration of either captopril or furosemide. There was no observed effect of oral conivaptan on the pharmacokinetics or pharmacodynamics of warfarin.<sup>47</sup> The effect of ketoconazole, a potent CYP3A4 inhibitor, on the serum levels of iv conivaptan has not been evaluated; however, co-administration of 10 mg oral conivaptan with 200 mg of ketoconazole resulted in a 4- and 11-fold increase in  $C_{max}$  and AUC of conivaptan, respectively. Co-administration of clarithromycin (a strong CYP3A4 inhibitor) and conivaptan can increase the exposure to conivaptan and potentiate its toxicity<sup>47</sup> (Table 3).

## Precautions, contraindications, side effects

Serum  $[Na^+]$  level should be strictly monitored during treatment to avoid overly rapid increase of serum  $[Na^+]$  and the possible serious permanent neurological complications. Conivaptan should be used with caution in patients with renal or liver impairment since it can be associated with increased systemic exposure and potential side effects.

In pregnant rats and rabbits, conivaptan administration has shown a delay in fetal growth, physical development and sexual maturation.<sup>43,47</sup> Therefore its use in pregnancy is classified as category C and should be used only if the potential

**Table 3** Medications with potential for significant drug interactions

<b>Chemotherapeutic agents</b>	<b>Calcium channel blockers</b>	<b>Others</b>
Doxorubicin	Amlodipine	Quinidine
Etoposide (BP-16)	Diltiazem	Buspirone
Tamoxifen	Felodipine	Zolpidem
Vinblastine	Isradipine	Nefazodone
Vincristine	Lercanidipine	Trazodone
	Nicardipine	Carbamazepine
	Nifedipine	Glucocorticoids
	Nimodipine	Rifabutin
	Nisoldipine	
	Nitrendipine	
	Verapamil	
<b>HMG CoA reductase inhibitors</b>	<b>Benzodiazepines</b>	<b>Macrolide antibiotics</b>
Atorvastatin >60 mg/day	Alprazolam	(except azithromycin, dirithromycin and roxithromycin)
Lovastatin	Diazepam	
Simvastatin	Midazolam	
Rosuvastatin	Triazolam	
<b>Protease inhibitors</b>	<b>Immunosuppressants</b>	<b>Azole antifungals</b> (except fluconazole and topical antifungals)
Ritonavir	Cyclosporine	
Indinavir	Tacrolimus	

benefit justifies the potential risk to the fetus. Conivaptan is also contraindicated in lactation as it has been found in the milk of lactating animals.<sup>47</sup>

Conivaptan is contraindicated in hypernatremia, hypovolemic hyponatremia, and in those who have hypersensitivity to any of its components. Co-administration of conivaptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir and indinavir is also contraindicated.<sup>47</sup> In patients with hypovolemia or total body fluid depletion, conivaptan can potentially precipitate renal failure, ischemic organ damage, and shock and thus it is contraindicated.<sup>47</sup>

Conivaptan administration is usually well tolerated. The most common adverse reaction reported with conivaptan administration was infusion site reaction (including pain, erythema, phlebitis and swelling). This occurred in 52.5% of subjects treated with conivaptan 40 mg/day compared to 3.3% in the placebo group, in studies involving patients and healthy volunteers, and it was the most common reason for discontinuation of treatment. A pilot study done among patients hospitalized with acute decompensated heart failure showed that infusion site reaction was the most reported side effect, and conivaptan was well tolerable among this patient population.<sup>48</sup> Other reported side effects in decreasing order included orthostatic hypotension, fever, hypokalemia, hypertension, hypotension, peripheral edema,

headache, hypomagnesaemia, constipation, diarrhea, nausea, vomiting, dry mouth, thirst, polyuria, oral candidiasis, pneumonia, urinary tract infection, insomnia and confusion. Conivaptan can also potentially precipitate renal failure, ischemic organ damage and shock. Common adverse reactions in 72 healthy volunteers and 243 patients with euvolemic and hypervolemic hyponatremia who received 20 mg iv conivaptan loading dose followed by 40 mg/day iv for 2 to 4 days were reported as follows: infusion site phlebitis (32%), infusion site reaction (19%), hypokalemia and headache (10%), peripheral edema (8%), vomiting and diarrhea (7%), anemia, constipation, infusion site erythema, thirst, hyponatremia, hypertension, and orthostatic hypotension (6%).<sup>49</sup>

### The risk of rapid correction of hyponatremia

Prompt and adequate treatment of hyponatremia is necessary to relieve early symptoms and prevent progression to seizures and irreversible brain damage. However rapid correction of hyponatremia may cause osmotic demyelinating syndrome (ODS), leading to permanent disability or death. In chronic hyponatremia, brain cells lose osmolytes, leading to movement of water out of the cells, a mechanism that offers protection from developing cerebral edema.<sup>50,51</sup> These osmolytes include [Na<sup>+</sup>], potassium and

organic solutes. Activation of cation channels leads to rapid movement of electrolytes whereas organic solute loss occurs later because it requires the synthesis of new transporters.<sup>52-54</sup> How ODS develops is not completely understood, however, the mechanism appears to be that osmolytes cannot be quickly replaced as the brain volume shrinks in response to an elevation in the plasma  $[Na^+]$  concentration.<sup>55</sup> As a result, it is currently recommended that the plasma  $[Na^+]$  concentration in hyponatremic patients be elevated at a maximum rate of 10 to 12 mEq/L during the first day and 18 mEq/L over the first 2 days.<sup>41,42</sup>

Rapid serum  $[Na^+]$  correction was defined in conivaptan clinical trials by the occurrence of any of the following 1) An increase in serum  $[Na^+] > 12$  mEq/L in 1 day; 2) a total increase in serum  $[Na^+]$  of more than 24 mEq/L; 3) serum  $[Na^+] > 145$  mEq/L; or 4) reduced or temporarily withheld treatment after an increase in serum  $[Na^+]$  judged to be too rapid. The reported prevalence of rapid correction in conivaptan clinical trials is 9% with no occurrence of permanent neurologic sequela. However, this prevalence was based mainly on one criterion, an increase of serum  $[Na^+] > 12$  mEq/L in 24 hours and the prevalence may be somewhat higher if all above mentioned definitions were

used. To date there has been no report of ODS with the use of conivaptan or any other VRAs.

## Conivaptan in the treatment of hyponatremia

### Animal studies

Antagonism of the  $V_2$  receptor increases free water excretion causing hypo-osmolar urine, enhanced diuresis, and increased plasma  $[Na^+]$  levels. Several animal studies have demonstrated the aquaretic effect of conivaptan (Table 4). Yatsu et al<sup>56</sup> showed in conscious dogs that the administration of both oral and iv conivaptan resulted in a dose-dependent aquaresis. Tomura et al<sup>57</sup> showed that oral conivaptan increased the urine volume and reduced the urine osmolality in dehydrated conscious rats and compared to furosemide the amount in  $[Na^+]$  excretion was much lower. In a study in normal conscious rats by Risvanis et al,<sup>44</sup> oral conivaptan caused a dose dependent increase in urine volume and fluid intake and decreased urine osmolality without natriuresis. Tahara et al<sup>45</sup> showed that iv administration of conivaptan increased urine volume and reduced urine osmolality in a dose dependent manner in dehydrated rats and Wada et al<sup>58</sup> showed that iv conivaptan produced statistically significant

**Table 4** Effect of conivaptan on urinary volume and  $[Na^+]$  concentration in animals

References	Species	Condition of species	Intervention	Results
Risvanis et al <sup>44</sup>	Rats (male Sprague-Dawley)	Normal Conscious	Vehicle or 1 mg/kg iv or 3 mg/kg oral conivaptan	Dose-dependent increase in urine volume and decrease in urine osmolality without natriuresis
Tahara et al <sup>45</sup>	Rats (male and female Wistar)	Dehydrated Conscious	Vehicle or 0.01 to 0.3 mg/kg iv conivaptan	Increased urine volume and reduced urine osmolality in a dose-dependent manner
Yatsu et al <sup>56</sup>	Dogs (female Beagle)	Normal Conscious	Oral 0.03 to 0.3 mg/kg or 0.01 to 0.1 mg/kg iv conivaptan or iv furosemide 0.3 mg/kg	Dose-dependent aquaresis
Tomura et al <sup>57</sup>	Rats (male Wistar)	Normal and dehydrated Conscious	1-dehydrated: 0.1, 0.3, 1, 3 mg/kg oral conivaptan or furosemide 3, 10, 30, 100 mg/kg 2-hydrated: vehicle or 0.3, 1, 3 mg/kg oral conivaptan or furosemide 100 mg/kg	(1) Dose-dependent increase in urine volume and reduction in urine osmolality. Increased urinary $[Na^+]$ excretion to a lower degree than furosemide (2) Dose-dependent increase in urine volume with longer duration of diuresis compared to furosemide
Wada et al <sup>58</sup>	Rats (n = 44) (male Wistar)	SIADH Conscious	Vehicle or 0.1, 1 mg/kg iv conivaptan vs Vehicle or furosemide 10 mg/kg	Increased both blood $[Na^+]$ concentration and plasma osmolality vs no effect of furosemide on either IV furosemide did not increase either blood $[Na^+]$ concentration or plasma osmolality

**Abbreviations:** iv, intravenous; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

increase in blood  $[\text{Na}^+]$  concentration and plasma osmolality in rats with SIADH.

## Human studies

The effects of conivaptan on serum  $[\text{Na}^+]$  in patients with euvolemic and hypervolemic hyponatremia have been studied in 3 randomized, double-blinded, placebo-controlled clinical trials (two with oral and one with iv conivaptan) and in one open label iv study (Table 5).

In a study by Ghali et al,<sup>59</sup> 74 patients with euvolemic or hypervolemic hyponatremia as defined by serum  $[\text{Na}^+]$  of 115 to  $<130$  mEq/L were stratified by volume status and assigned randomly in 1:1:1 ratio to receive oral placebo, 40 mg/day or 80 mg/day conivaptan in 2 divided doses. Euvolemic hyponatremia was present in 75% of patients. The primary efficacy end point was the change from baseline in serum  $[\text{Na}^+]$  throughout the 5 days of treatment, as measured by the serum  $[\text{Na}^+]$  AUC. The conivaptan groups, 40 and 80 mg/day had least square (LS) mean change from baseline in serum  $[\text{Na}^+]$  AUC during the 5-day treatment that was 2-fold ( $P = 0.03$ ) and 2.5-fold ( $P < 0.001$ ) greater, respectively, than placebo. Also, the efficacy on secondary end points was consistent including shorter median time to achieve a confirmed increase in serum  $[\text{Na}^+]$  of 4 mEq/L or more from baseline ( $P < 0.044$  for the 40 mg/day and  $P < 0.002$  for the 80 mg/day conivaptan), a longer mean total times during which patients had a serum  $[\text{Na}^+]$  level of 4 mEq/L or more above baseline ( $P < 0.001$ ), a greater LS mean change in serum  $[\text{Na}^+]$  from baseline to end of treatment ( $P < 0.002$ ) and a higher percentage of a confirmed normal serum  $[\text{Na}^+] \geq 135$  mEq/L or increase of 6 mEq/L or more ( $P < 0.014$ ).

In the recently published multicenter European study by Annane et al<sup>60</sup> 83 patients with euvolemic or hypervolemic hyponatremia with serum  $[\text{Na}^+] < 130$  mEq/L, plasma osmolality  $<290$  mOsmol/kg  $\text{H}_2\text{O}$  and no evidence of extracellular volume depletion were divided into three different groups and received conivaptan 20 mg twice daily (40 mg/day), conivaptan 40 mg twice daily (80 mg/day), or placebo for 5 days as inpatients. All patients were prescribed fluid restriction and diuretic doses were stabilized before screening and remained constant throughout the study. Euvolemic hyponatremia was present in 63% at baseline, and the most common single causes of hyponatremia were heart failure (33%) and cancer (17%). The primary efficacy end point was the change from baseline in serum  $[\text{Na}^+]$

throughout the 5 days of treatment, as measured by the serum  $[\text{Na}^+]$  AUC. Conivaptan produced a dose-dependent and significantly greater increase in serum  $[\text{Na}^+]$  AUC than placebo ( $P < 0.0001$ ). The difference in serum  $[\text{Na}^+]$  AUC between the 2 conivaptan doses was also statistically significant ( $P < 0.028$ ).

The efficacy on secondary endpoints was also consistent. Both doses of conivaptan achieved shorter median times from the first dose to a confirmed serum  $[\text{Na}^+]$  increase of 4 mEq/L or greater from baseline ( $P < 0.0004$  for the 40 mg/day and  $P < 0.0001$  for the conivaptan 80 mg/day). Both groups were significantly different from the placebo group. The median time was not estimable in the placebo group (too few patients achieved an increase of 4 mEq/L or greater during the 5-day study). Moreover, the LS mean total time during which patients had an increase in serum  $[\text{Na}^+]$  of 4 mEq/L or more from baseline was significantly greater among patients given conivaptan 40 mg/day and 80 mg/day compared to placebo ( $P < 0.0001$ ).

Both doses of conivaptan had greater LS mean  $\pm$  SE change in serum  $[\text{Na}^+]$  from baseline to the end of treatment ( $P < 0.0001$ ). Similarly, both doses of conivaptan groups had a higher number of patients who demonstrated either a confirmed serum  $[\text{Na}^+]$  of 6 mEq/L or more above baseline or normal serum  $[\text{Na}^+] (\geq 135$  mEq/L) ( $P < 0.0008$  for the 40 mg/day vs  $P < 0.001$  for the conivaptan 80 mg/day). Of note, 7 days after the study ended, both conivaptan groups had higher change in serum  $[\text{Na}^+]$  than those in placebo group. Finally, conivaptan, in comparison with placebo, produced greater increases in free and effective water clearance, net fluid loss, plasma osmolality and greater reductions in urine osmolality and urine  $[\text{Na}^+]$  levels.

Iv conivaptan has been shown to have similar effects on serum  $[\text{Na}^+]$ . In a study by Zeltser et al,<sup>61</sup> 84 patients hospitalized with euvolemic and hypervolemic hyponatremia, with serum  $[\text{Na}^+]$  of 115 mEq/L to  $<130$  mEq/L were randomized to receive placebo or 20 mg of conivaptan as a bolus iv dose, followed by a continuous infusion of 40 or 80 mg per day for 4 days. Both conivaptan doses increased  $[\text{Na}^+]$  AUC during the 4-day treatment ( $P < 0.0001$  vs placebo) and the LS mean changes in serum  $[\text{Na}^+]$  at day 4 for the 3 respective groups were significantly greater with conivaptan ( $P < 0.001$ ) and so was the percentage of patients achieving 6 mEq/L or more increase in serum  $[\text{Na}^+]$  from baseline or normalization of  $[\text{Na}^+]$  (defined as  $\geq 135$  mEq/L) ( $P < 0.001$ ). The median time from the



first dose to 4 mEq/L increase in serum  $[Na^+]$  was 23.7 hours and 23.4 hours for the conivaptan 40 mg/day and 80 mg/day groups, respectively ( $P < 0.001$ ).

In all of these randomized studies, the magnitude of changes in serum  $[Na^+]$  was clinically significant. One might speculate that the design of these studies could have been benefited by separating the included patient population by the etiology of hyponatremia or by stratifying randomization by etiology (heart failure vs SIADH). In addition, detailed information on fluid input and output would have provided additional information. Finally, a serial measurement of serum  $[Na^+]$  over extent period of time would have shed light on the duration of corrected hyponatremia and the frequency with which it persists.

Verbalis et al conducted an open-label trial<sup>62</sup> investigating 4 days treatment with iv conivaptan. The magnitude of changes in serum  $[Na^+]$  sodium is clinically significant: 20 mg/day ( $n = 37$ ) or 40 mg/day ( $n = 214$ ) in patients with euvolemic or hypervolemic hyponatremia. Patients received a loading dose of iv conivaptan 20 mg as a 30-minute infusion followed by a continuous iv infusion of conivaptan 20 or 40 mg/day for 4 days. The primary efficacy point was base-line adjusted serum  $[Na^+]$  area under the curve over the duration of treatment, which was 753.8 mEq · h/L +429.9 in the 20 mg/day group and 689.2 mEq · h/L + 417.3 in the 40 mg/day group.

Only iv conivaptan has been approved for use in hospitalized patients with euvolemic and hypervolemic hyponatremia. The development of the oral formulation was stopped because of multiple drug–drug interactions due to inhibition of CYP3A4 in intestine and liver that is involved in the metabolism of many drugs especially cardiovascular medications.

## Use of conivaptan in heart failure

Heart failure is characterized by neurohormonal activation that plays a central role in  $[Na^+]$  and water retention. Several mechanisms mediate volume overload and hyponatremia in heart failure, and both hyponatremia and congestion share many common pathophysiological pathways including activation of the SNS, the RAAS and AVP.<sup>24</sup> Antagonism of the multiple actions mediated by AVP and the potential beneficial effect of conivaptan in heart failure has been investigated in several studies.

## Animal studies

AVP has been shown, through the activation of  $V_{1A}$  receptor, to increase the rate of protein synthesis in the myocardium

leading to myocyte hypertrophy in rats<sup>63–66</sup> (Table 6). In a study by Tahara et al,<sup>65</sup> conivaptan was demonstrated to have dose-dependent inhibition of the AVP-induced protein synthesis in neonatal rat cardiomyocytes. Similar effects of conivaptan were demonstrated in another study by Tahara et al<sup>65</sup> in rat vascular smooth muscles.<sup>66</sup>

The effects of conivaptan on the hemodynamics in heart failure have also been studied in multiple animal models (Table 6).

Conivaptan reversed the decrease in cardiac output and the increase in total peripheral resistance induced by AVP in dogs without heart failure.<sup>67</sup> In a dog model with pacing induced heart failure, iv conivaptan increased cardiac output and stroke volume, reduced preload and afterload, increased urine flow and decreased urine osmolality.<sup>68</sup>

In rats with myocardial infarction induced heart failure, both oral and iv conivaptan increased myocardial contractility and reduced right atrial and both right and left ventricular end diastolic pressures compared to control.<sup>69</sup> It also increased urine volume and reduced urine osmolality in rats with and without coronary heart failure.<sup>70</sup>

## Human studies (Table 7)

Several studies have been performed to assess the effects of conivaptan in heart failure (Table 7). A hemodynamic double-blinded, randomized, placebo-controlled study of 142 patients with heart failure (NYHA class III and IV) receiving a single dose of iv conivaptan demonstrated a significant reduction in pulmonary capillary wedge pressures ( $P < 0.05$ ) and right atrial pressure ( $P < 0.05$ ) compared to placebo. The hemodynamic improvements were accompanied by increased urine output ( $P < 0.001$ ) without affecting renal function. There were no significant changes in cardiac index, systemic and pulmonary vascular resistance, blood pressure and heart rate compared to placebo.<sup>71</sup>

The effects of conivaptan on heart failure symptoms and functional capacity were evaluated in a 12-week oral administration study, A Dose Evaluation of a Vasopressin Antagonist in CHF Patients undergoing Exercise (ADVANCE).<sup>72</sup> Among 345 patients with class II–IV heart failure, randomized to oral conivaptan 10, 20, 40 mg twice daily or placebo, there was no significant difference in exercise tolerance, as measured by the time to reach 70% of peak oxygen consumption, between conivaptan and placebo.

In recent double blinded, multicenter study,<sup>48</sup> the use of conivaptan was evaluated in 170 patients admitted with acute decompensated heart failure with worsening dyspnea and pulmonary vascular congestion. The mean age was

**Table 5** Conivaptan studies in patients with hyponatremia

Baseline Na <sup>+</sup>	Ghali et al <sup>59</sup>			Annane et al <sup>60</sup>			Zeltser et al <sup>61</sup>		
<b>Total number of patients</b>	74			83			84		
<b>Ethnicity</b>	89% Whites			100% Whites			85.7% Whites		
<b>Females</b>	51.4%			33.7%			51.2%		
<b>Age &gt; 65</b>	68%			47%			71.4%		
<b>Age</b>	–			–			–		
<b>Euvolemic %</b>	75%			62.7%			66.7%		
<b>Design</b>	Double-blinded, placebo-controlled			Double-blinded, placebo-controlled			Double-blinded, placebo-controlled		
<b>iv or oral conivaptan</b>	Oral			Oral			iv		
<b>Dose of conivaptan</b>	Placebo or conivaptan 40 or 80 mg/d in 2 divided doses			Placebo or conivaptan 40 or 80 mg/d in 2 divided doses			Placebo or 20 mg of conivaptan as a bolus iv dose, followed by a continuous infusion of 40 or 80 mg/d		
<b>Duration of treatment</b>	5 days			5 days			4 days		
<b>Primary endpoint</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>
LS mean change from baseline in serum [Na <sup>+</sup> ]	309.2	621.3 (0.03)	836.2 (<0.001)	88 ± 81	634 ± 84 (0.0001)	953 ± 86 (0.0001)	12.9	490.9 (<0.001)	716.6 (<0.001)
AUC during the 5-day treatment ± SE (mEq h/L)									
<b>Secondary endpoints</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>	<b>Placebo</b>	<b>40 mg/d (P)</b>	<b>80 mg/d (P)</b>
Time to a confirmed increase in serum [Na <sup>+</sup> ] ≥ 4 mEq/L from baseline (median h)	71.7	27.5 (0.044)	12.1 (0.002)	–	23.5 (0.0004)	8.7 (0.0001)	–	23.7 (<0.001)	23.4 (<0.001)
Total time serum [Na <sup>+</sup> ] ≥ 4 mEq/L above baseline [LS mean (SE)-h]	46.5	69.8 (0.103)	88.8 (0.001)	20.3	68.8 (0.0001)	86.6 (0.0001)	14.2	53.2 (<0.001)	72.7 (<0.001)
Change in serum [Na <sup>+</sup> ] to end of treatment [LS mean (SE) mEq/L]	3.4	6.4 (0.081)	8.2 (0.002)	1.6	7.2 (0.0001)	9.1 (0.0001)	0.8	6.3 (<0.001)	9.4 (<0.001)
Patients with a confirmed normal serum [Na <sup>+</sup> ] (≥ 135 mEq/L) or increase of ≥6 mEq/L [no. (%)]	11	17 (0.111)	22 (0.014)	20	66.7 (0.0008)	88.5 (<0.0001)	20.7	69 (<0.001)	23 (<0.001)

63.5 years and 63% were males. The mean left ventricular ejection fraction was 29.5% and 91% had NYHA class III and IV heart failure. Patients were randomized to receive 20 mg conivaptan or placebo loading dose, followed by 40, 80, or 120 mg/day conivaptan or placebo by continuous iv infusion for 2 days. Despite the increase in total urine output ( $P < 0.02$ ) and the trend for a decrease in body weight), patient-assessed severity of respiratory symptoms did not improve.

A pooled analysis of a randomized controlled trial<sup>61</sup> and an open-label trial<sup>62</sup> evaluated the efficacy and safety of conivaptan in 335 patients with euvolemic or hypervolemic hyponatremia with or without underlying heart failure. Conivaptan (20 mg loading dose followed by 4-day continuous infusion of 40 or 80 mg/day in the randomized controlled trial and 20 or 40 mg/day in the open-label trial) produced prompt but controlled increases in serum [Na<sup>+</sup>]

Verbalis et al <sup>62</sup>	Ghali et al <sup>73</sup>								
	HF 98				No HF 237				
251									
–	Placebo	20 mg	40 mg	80 mg	Placebo	20 mg	40 mg	80 mg (Whites)	
–	78	90	83	63	95	85	92	78	
–	44	60	54	38	50	67	70	50	
–	89	80	79	63	90	89	74	78	
–	75.7	69	73.1	70.8	75.7	75.1	71.7	73.7	
–									
Open label	Double-blind placebo-controlled (n = 184) open label (n = 251)								
iv	iv								
Loading dose of iv conivaptan 20 mg followed by a continuous iv infusion of conivaptan 20 or 40 mg/d	Loading dose of 20 mg followed by continuous infusion 40 or 80 mg/d								
4 days	4 days				4 days				
<b>20 mg/d</b> <b>80 mg/d</b>	<b>Placebo</b>	<b>20 mg/d</b>	<b>40 mg/d</b>	<b>80 mg/d</b>	<b>Placebo</b>	<b>20 mg/d</b>	<b>40 mg/d</b>	<b>80 mg/d</b>	
753.8   689.2	93	459.0	579.0	576.0	47.0	867.0	703.0	700.0	
<b>20 mg/d</b> <b>80 mg/d</b>	<b>Placebo</b>	<b>20 mg/d</b>	<b>40 mg/d</b>	<b>80 mg/d</b>	<b>Placebo</b>	<b>20 mg/d</b>	<b>40 mg/d</b>	<b>80 mg/d</b>	
–   –	NE	30.0	28.0	24.0	NE	18.0	24.0	8.0	
–   –									
–   –	3.0	7.9	7.9	9.0	3.1	9.8	8.1	9.4	
–   –	11	50	63	88	25	78	75	89	

**Abbreviations:** AUC, area under the curve; iv, intravenous; HF, heart failure; NE, not estimable.

that were often evident by the end of day 1 of treatment. By the end of treatment most conivaptan-treated patients with or without heart failure achieved a  $\geq 6$  mEq/L increase in serum  $[\text{Na}^+]$  above baseline or a normal serum  $[\text{Na}^+]$  concentration ( $\geq 135$  mEq/L).

Patients with heart failure demonstrated a lower increase in serum  $[\text{Na}^+]$  AUC, a longer time to a confirmed  $\geq 4$  mEq/L increase in serum  $[\text{Na}^+]$ , and a lower

likelihood of a  $\geq 6$  mEq/L increase in serum  $[\text{Na}^+]$  or a normal serum  $[\text{Na}^+]$  compared to those without heart failure.

Another issue that has not been adequately addressed is fluid restriction. On one hand, adherence to strict fluid restriction may result in hyponatremia but on the other, liberalization of fluid intake may limit the extent of fluid removal in patients with decompensated heart failure and fluid overload.

**Table 6** Effect of conivaptan on myocardial cells hemodynamics in heart failure animals

References	Species	Condition of species	Intervention	Results
Tahara et al <sup>65</sup>	Neonatal rat cardiomyocytes (Wistar rats)	Cultured cells	YM087 (conivaptan)	Dose dependent inhibition of AVP induced protein synthesis
Tahara et al <sup>66</sup>	Rat vascular smooth muscle cells	Cultured cells	YM087 (conivaptan)	Prevented AVP-induced hyperplasia and hypertrophy of these cells in concentration dependent manner
Yatsu et al <sup>67</sup>	Dogs (n = 8) (male and female Beagle)	Pacing-induced HF Anesthetized	Vehicle or 0.1 mg/kg iv conivaptan	Increased cardiac output and stroke volume, reduced LVEDP and TPR, increased urine flow and decreased urine osmolarity
Yatsu et al <sup>68</sup>	Dogs (n = 11) (male and female mongrel dogs)	Normal Anesthetized	AVP infusion followed by iv bolus of 0.9% saline followed by 0.1 mg/kg iv conivaptan	Rapidly attenuated the AVP induced decrease in CO and reversed the AVP induced elevation in both LVEDP and TPR
Wada et al <sup>69</sup>	Rats	MI-induced HF (n = 30) Conscious vs Sham operated control rats Conscious	Aquaretic effect: (n = 30) Vehicle or 0.03, 0.1, 0.3 mg/kg iv conivaptan Or 0.3 mg/kg V <sub>2</sub> R antagonist SR121463A Hemodynamic effect: (n = 39) Vehicle or 0.1, 0.3 mg/kg iv conivaptan Or 0.3 mg/kg V <sub>2</sub> R antagonist SR121463A	Dose dependent increase in urine volume and reduction of urine osmolality in both HF and sham-operated rats. SR121463A had similar effects to conivaptan Reduction of RV systolic and RA pressures, LVEDP, lung and body weight. Increased dP/dt <sub>max</sub> /LVP SR121463A caused similar effects except it did not improve dP/dt <sub>max</sub> /LVP
Wada et al <sup>70</sup>	Rats (n = 19) (male Wistar)	MI-induced HF vs Sham operated control rats Conscious	Aquaretic effect: Vehicle or 0.3 to 3 mg/kg oral conivaptan Hemodynamic effect: Vehicle or 3 mg/kg oral conivaptan	Higher AVP level in HF compared to sham operated rats Reduction of LVEDP, lung and RV weights and reduced mean blood pressure. No effect on heart rate or LV systolic pressure Conivaptan also increased urine volume and reduced urine osmolarity

**Abbreviations:** AVP, arginine vasopressin peptide; CO, cardiac output; HF, heart failure; iv, intravenous; LV, left ventricle; LVP, left ventricular pressure; LVEDP, left ventricle end diastolic pressure; MI, myocardial infarction; RA, right atrium; RV, right ventricle; TPR, total peripheral resistance.

## Use of conivaptan in cirrhosis

Cirrhosis, like heart failure, is characterized by dilutional hyponatremia, impaired water excretion and persistent inappropriate AVP elevation by non-osmotic mechanisms. There is limited information about the use of conivaptan in this setting. In one study in rats with cirrhosis, conivaptan has shown to increase urine volume and osmolarity without affecting arterial blood pressure and creatinine clearance.<sup>74</sup> Theoretically, it may not be advisable to use conivaptan in patients with cirrhosis because of the possibility that V<sub>1A</sub> inhibition may result in splanchnic vasodilatation as well as interference with platelet aggregation, actions that may promote variceal bleeding.<sup>32</sup>

## Other uses of AVP receptor blockers

### Hyponatremia in the neurocritical care unit

The use of conivaptan in correcting hyponatremia in patients admitted to neurointensive care units was reported in two

retrospective studies. The first study in 22 patients with hyponatremia (defined as [Na<sup>+</sup>] < 136 mEq/L) showed a very favorable response to conivaptan given as a bolus followed by infusion. An increase of ≥6 mEq/L was noted in 86% of the patients with an average time of 13.1 hours and no patient experienced rapid over correction.<sup>75</sup> In another study, correction of hyponatremia was evaluated in 19 patients admitted to a neurointensive care unit with the administration of conivaptan 20 or 40 mg bolus given over 30 minutes, and repeated bolus injections given 12 to 72 hours after the first with no subsequent infusion. Serum [Na<sup>+</sup>] increased by 5.8 ± 3.2 mEq/L within 12 hours for an overall 71% response as defined by at least 4 mEq/L increase in serum [Na<sup>+</sup>] and 52% manifesting a 6 mEq/L. An increase of 4 mEq/L was maintained for up to 72 hours in 69% of patients.<sup>76</sup>

### Tumor lysis syndrome

Conivaptan was used to treat SIADH in a thirteen year-old patient with large-cell lymphoma before and during

Table 7 Conivaptan human studies in heart failure

References	Design	Intervention	Measurements	Number of patients	Condition of patients	Major results
Goldsmith et al <sup>48</sup>	Double-blind, placebo-controlled, randomized pilot trial	IV conivaptan (20 mg loading dose followed by 40, 80 or 120 mg/d continuous infusion for 2 days	AUC change from baseline at 48 h in patient-assessed severity of respiratory symptoms and global status Total urine output at 72 h The total daily urine output at 24, 48, and 72 h The change from baseline in body weight at 24, 48, and 72 h Patient and clinician global assessments and dyspnea assessments Comparison of clinical signs of heart failure with baseline findings was also recorded.	170	Acute Decompensated HF	Increased total urine output ( $P = 0.02$ ) and decreased body weight (not significant) Did not improve patient-assessed severity of respiratory symptoms Clinical signs of heart failure were improved consistently in all groups on day 30
Udelson et al <sup>71</sup>	Double-blinded placebo-controlled randomized trial	Single dose of 10, 20 or 40 mg iv conivaptan	Hemodynamics and urine volume	142	NYHA class III and IV	Reduced PCWP ( $P < 0.05$ ) and RAP ( $P < 0.05$ ) when compared to placebo. Increased urine output ( $P < 0.001$ ) without affecting renal function. There were no significant changes in cardiac index, systemic and pulmonary vascular resistance, blood pressure and heart rate compared to placebo
Russell et al <sup>72</sup>	Double-blind, placebo-controlled, randomized trial	12-week 10, 20, 40 mg bid oral conivaptan	Exercise time to reach 70% of peak oxygen consumption during an incremental exercise test	345	NYHA class II-IV	No significant differences in exercise tolerance between conivaptan and placebo

**Abbreviations:** AUC, area under the curve; HF, heart failure; iv, intravenous; NYHA, New York Heart Association; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure.

chemotherapy administration. This allowed aggressive hydration to prevent tumor lysis syndrome while inducing free-water excretion.<sup>77</sup> Further studies are needed to assess the potential therapeutic use for conivaptan for this indication.

## Future use of conivaptan

Conivaptan is distinguished from other VRAs by its antagonism of both  $V_{1A}$  and  $V_2$  receptors; thus, in heart failure it offers a theoretical advantage by combining a potential of hemodynamic benefit and reverse remodeling in addition to diuresis. Experimentally, it has been demonstrated that combined antagonism of  $V_{1A}$  and  $V_2$  receptors could induce more beneficial hemodynamic responses compared to antagonism of  $V_{1A}$  receptors alone.<sup>78</sup> Also, it is worth mentioning that in the single dose hemodynamic study, there was no correlation between urine output and the decrease in filling pressures suggesting the possibility of a salutary effect beyond diuresis. Furthermore, that study was carried on in stable patients with heart failure, therefore, the potential benefit of conivaptan in patients with acute decompensated heart failure, whether systolic or diastolic and particularly in those with hyponatremia has not been adequately explored and it should be further investigated.

The ability to administer conivaptan intravenously offers an opportunity to explore its usage in the treatment of symptomatic hyponatremia in combination with hypertonic saline. Considering the ease of use of single or multiple injections rather than continuous infusion, the efficacy of this modality of administration should also be investigated.

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