Aquaretics Use in Acute Decompensated Heart Failure (ADHF) Patients: A Literature Review

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ABSTRACT

This is a literature review of the use of aquaretic in patients with acute decompensated heart failure (ADHF), including the physiologic function of vasopressin and its mechanism of action in heart failure patients, and aquaretic drugs with their respective risks and benefits.

Vasopressin is one of several hormones that can cause hyponatremia and worsen congestion in ADHF patients. Aquaretics are a class of drugs that have an antagonistic effect on vasopressin receptors, especially V2R. Aquaretics use in ADHF patients can provide relief for congestive symptoms with no serious adverse effects. In-depth additional understanding regarding aquaretics may be useful for clinical judgments in treating ADHF patients.

Keywords*: acute decompensated heart failure (ADHF), aquaretics.*

INTRODUCTION

Heart failure is a global pandemic, with a rapidly increasing prevalence, affecting at least 26 million people worldwide.[1] In the United States of America, the *American Heart Association* (AHA) estimated that, between 2013 and 2016, around 6.2 million people suffered from heart failure. This number is projected to increase in 2030, with an increased prevalence rate of 46% from the available data in 2012, more than 8 million patients will have heart failure. This burden of disease will increase from 30.7 billion US dollars in 2012 to 69.8 billion US dollars in 2030.[2]

Generally, acute heart failure (AHF) is defined as a rapid onset or worsening of heart failure signs and symptoms that need urgent medical treatment. AHF may present as a first occurrence (*de novo)*, or more frequently, due to acute decompensation of chronic heart failure, commonly known as acute decompensated heart failure (ADHF).[3] More than 1 million hospitalizations per year in the United States is due to ADHF; thus, this condition is the main reason for hospitalization in patients aged 65 or more.[4] ADHF causes a heavy financial burden on the healthcare system, most of which are closely related to hospitalization. The in-hospital mortality rate of ADHF is around 4-7%; the 3-month post-discharge mortality rate is around 7-11%, and the 1-year post-discharge mortality rate is 36%. According to studies in the United States, the length of hospitalization is around four days, and in Europe, it can be around 6-11 days. Despite this long-standing burden, only a few steps were achieved within the last couple of years in medical treatment for ADHF.[5]

The management of ADHF was written by the European Society of Cardiology (ESC) in

2016 and the American College of Cardiology Foundation (ACCF) in conjunction with the AHA in 2013. However, aquaretic (vasopressin receptor antagonist) use was only considered in patients with volume overload and severe resistant hyponatremia.[3,6]

One of the pathophysiologies in heart failure patients is an increased level of vasopressin. Through the activation of the V1 pathway, there is an increase in peripheral resistance and pulmonary capillary wedge pressure (PCWP), whereas stroke volume and cardiac output decrease.[7] Vasopressin receptor antagonist drugs bind three receptors, V1R that affects vasoconstriction, V2R that has a role in water reabsorption, and V3R that affects the adrenocorticotropic hormone.[8] This literature review highlights the mechanism, benefits, risks, and use of aquaretics in ADHF patients.

PHYSIOLOGY OF VASOPRESSIN

Vasopressin, or antidiuretic hormone (ADH), is a hormone secreted in the hypothalamus and stored in the posterior pituitary. This hormone has several roles in controlling the body's osmotic balance, blood pressure regulation, sodium homeostasis, and kidney function.[9] These V receptors can be classified into V1 vascular (V1R), V2 renal (V2R), V3 pituitary (V3R), dan oxytocin (OTR) subtypes.[10]

V1R receptors are found in vascular smooth muscles and result in vasoconstriction by increasing the intracellular calcium levels. V1R receptors are also found in the brain, testes, liver, and renal medulla; however, the function is still unknown. Platelets are known to express V1R receptors, which facilitate thrombosis; however, there is varying platelet aggregation response in different individuals.[11]

V2R receptors are G-protein-coupled receptors (GPCR) found in the basolateral plasma membrane in the collecting duct. Vasopressin bound to this receptor will increase water absorption by regulating aquaporin-2 (AQP-2).[12] AQP-2 plays a crucial role in regulating short- and long-term water permeability in the collecting duct. Short-term regulation results in increased water permeability 5 to 30 minutes after vasopressin concentration increases, while the long-term regulation happens when vasopressin level increases within days, causing increased AQP2 levels in cells.[13] V3R correlates with the secretion of ACTH by binding the receptors in the anterior pituitary.[14] **Table 1** describes the vasopressin receptor's physiological effects.

VASOPRESSIN IN HEART FAILURE

Vasopressin levels will increase in heart failure patients as the functional severity of the disease increases.[15] The increase in vasopressin is modulated by three mechanisms: the osmoreceptor, the baroreceptor, and the renin-angiotensin-aldosterone system (RAS). Vasopressin production is primarily regulated by the osmoreceptors in the hypothalamus; a 1-2% decrease in plasma osmolality will suppress vasopressin level so that maximal aquaresis is achieved. Heart failure patients have a decreased cardiac output that causes lower arterial filling, leading to baroreceptor activation in the carotid sinus, aortic arch, and left ventricle. This pathway has a lower sensitivity in regulating vasopressin but is much more potent in heart failure patients. On the other hand, the RAS system regulates the vasopressin by direct secretion of the hormone angiotensin II.[16]

The increase in vasopressin leads to lower excretion of water and, thus, causes

Table 1. Physiologic Function of Vasopressin Receptor.[11–14]

Vasopressin Receptor	Location	Physiologic Function
V1R	Vascular smooth muscle (mainly), thrombocyte, brain, testicles, liver, cardiomyocyte, and kidney medulla	Vasoconstriction (mainly), gluconeogenesis, and thrombocyte aggregation
V2R	Collecting duct of the kidney	Increasing water reabsorption through AQP2
V3R	Anterior pituitary gland	Secreting ACTH

hyponatremia. Water retention will exacerbate congestion in heart failure patients, while hyponatremia independently correlates with increased mortality. Chronically, this process will cause heart remodeling.[17] (**Figure 1**)

PHARMACOLOGY OF AQUARETICS

Aquaretics are a class of drugs that induces water excretion without electrolyte excretion. This group of drugs refers to vasopressin receptor antagonists, especially V2 receptor antagonist.[19] Peptide vasopressin receptor antagonists have been developed since 1960; however, their efficacy is low. Peptide antagonists lose their antagonistic effects and become agonists when administered chronically and can only be given parenterally. Vaptan is a non-peptide vasopressin receptor antagonist that is orally active.[20] **Table 2** shows the available aquaretics.

Conivaptan is a type of vaptan with affinity to V1 and V2 receptors, with dose-dependent effects. Conivaptan is approved by the Food and Drug Administration (FDA) for its hyponatremia usage with an intravenous dose of 40-80 mg/day. However, this is not recommended for heart failure patients because no significant difference in the effect found when applied in the patients compared to placebo.[21]

Lixivaptan is an orally active vasopressin receptor antagonist with non-peptide and V2 receptor-selective (100:1 with V1) characteristics. Similar to Conivaptan, the potency of aquaresis in Lixivaptan is also dose-dependent.[22] Currently, this drug is undergoing phase 3 clinical trials in patients with autosomal dominant polycystic kidney disease (ADPKD).[23]

Mozavaptan (OPC-21268) is a selective V2 receptor antagonist (10:1 with V1), which can be given parenterally. The aquaretic effect from mozavaptan is dose-dependent (0,017-1 mg/kg) and still has its effect after two hours. When administered in high doses (0,75-1 mg/kg), its aquaretic effect has the same potency as 20 mg furosemide.[21] Mozavaptan is only used in Japan, and its clinical indication is for the inappropriate secretion of antidiuretic hormone in paraneoplastic syndrome.[20]

Satavaptan is an orally active and highly selective V2 receptor antagonist (112:1 with V1).[24] Satavaptan has a long half-life and can be

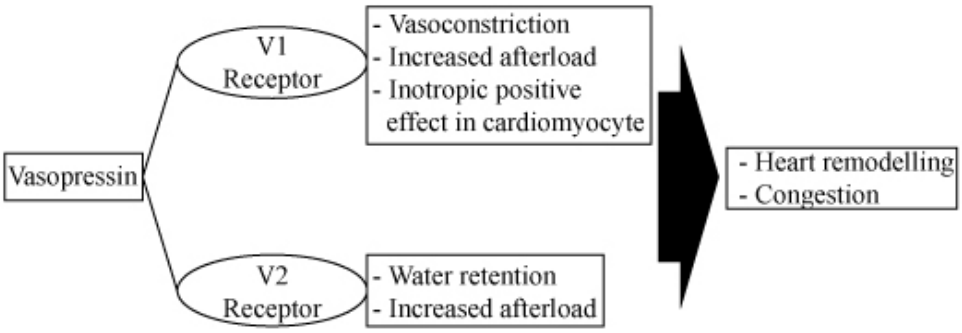

Figure 1. Role of vasopressin in heart failure.

Table 2. Aquaretics type available.[20]

Receptor Antagonist Type	Examples
V1/V2	Conivaptan
V2	Lixivaptan
	Mozavaptan
	Satavaptan
	Tolvaptan

given once daily with a 5-50 mg/day dose. This drug is metabolized in the liver and eliminated with the feces.[20]

Tolvaptan is a type of aquaretic with high selectivity to the V2 receptor (29:1 with V1) and has no biologic activity with V3. Around 40% of oral Tolvaptan dose will be reabsorbed, with maximal concentration achieved in 2-4 hours (not affected by foods). Dosing of tolvaptan starts from 15 mg once daily, and may only be increased after 24 hours until a maximum dose of 60 mg/day.[25] Tolvaptan is one of the few drugs accepted by the FDA for the treatment in hyponatremia in SIADH, heart failure, and liver failure patients because of its safety and efficacy. On the contrary, other vaptans are still under clinical trials or have already been rejected because of its safety and efficacy.[26]

BENEFITS AND USES

Decompensation in ADHF patients occurs due to increased sympathetic nervous system activation, ADH, and renin-angiotensin-aldosterone (RAAS). These neurohormonal activations cause upregulation in the RAAS and intrarenal vasoconstriction, thus increasing sodium and water retention. Diuretics such as furosemide, metolazone, and spironolactone have become one of the mainstay therapies for ADHF patients. Aquaretics are added to increase fluid and osmotic balance by inhibiting water retention without affecting the electrolytes in ADHF patients.[27]

Efficacy

Most patients hospitalized for ADHF are complaining about their symptoms due to volume overload (congestion). Decongestion through diuresis is one of the primary treatment in these patients, and some parameters such as weight loss, and urine output could be attributed as objective parameters to assess the efficacy. ACTIV trial, a randomized clinical trial (RCT) done by Gheorghiade *et al.* compared three doses of tolvaptan (30 mg, 60 mg, and 90 mg) with placebo. Patients aged 18 years and older with decompensated heart failure with stable hemodynamic were included. Tolvaptan was useful in weight loss on day one and significantly provided relief for congestive symptoms. An increase in sodium level was found in patients with a Tolvaptan regimen, while a small decrease was found in patients with a placebo regimen. Tolvaptan used in adjunction to standard therapies such as potassium-sparing diuretics will allow greater diuresis independent of the dose.[28]

This greater diuresis effect is reflected by one of the symptoms which is dyspnea. A meta-analysis from Luo et al, stated add-on tolvaptan was shown to be more effective in relieving short-term dyspnea than traditional diuretics alone (RR = 1.12 [1.05-1.18]). In addition to relieving dyspnea, tolvaptan as an add-on therapy was also more effective at reducing edema and body weight, as well as urine output (RR = 1.08 [1.02-1.15], MD = -0.82 [-0.94 – 0.71], MD = 0.49 [0.39 – 9.60] respectively).[29] This finding is similar with meta-analysis from Ma, et al, which included 7 RCT with 937 patients showed that Tolvaptan as an adjuvant therapy may reduce body weight and increase sodium levels in ADHF patients significantly.[30]

In contrast, TACTICS-HF by Felker, et al showed that, despite of greater weight loss and net fluid loss in the tolvaptan arm compared in placebo, but dyspnea relief by Likert scale was similar between these 2 arms at 8 hour and 24 hour (p: 0.59, and 0.80 respectively). These 2 arms were received standardized loop diuretic which consist of IV furosemide equivalent to their total daily oral outpatient dose (low dose arm in DOSE study). These findings may represent that despite net fluid loss is higher, time is needed for distribution of fluid out of the extravascular spaces into the circulation. Median length of stay was similar in both groups (5 days), and other clinical endpoints such as post-discharge outcome in 30 days was similar.[31] Konstam, et al has similar finding in his RCT, which tolvaptan has rapid and persistent weight loss, but not associated with improvement in dyspnea at first 8 – 24 hours (assessed with Likert dyspnea scores), but at day 3 dyspnea reduction was greater and significant in tolvaptan arm.[32] These findings suggest that further research is needed to develop more strategies for decongestion in patients with ADHF.

Loop diuretic is the mainstay therapy for congestion in patients with ADHF and tolvaptan add-on has shown great efficacy to relieve the congestion, but tolvaptan has been studied as monotherapy in patient with ADHF. AQUA-AHF, a randomized pilot study conducted by Ng et al, evaluating tolvaptan as monotherapy (30 mg oral, daily) in patients with HF that required hospitalization for decongestive therapy with hyponatremia compared to loop diuretics (5mg/h IV). This study showed that urine output, and net fluid balance were better in the furosemide group, but did not have significant differences in median between groups. Renal function is also better in the furosemide group, but not statistically significant. Oral tolvaptan monotherapy was associated with similar diuresis compared with IV furosemide, but not superior.[33] Larger studies are needed to further address this finding.

Diuretic resistance (DR) is a common challenge in treating ADHF patients. Patients with such condition are commonly treated with a combination of diuretic regiments. Current guidelines recommend adding a second diuretic such as thiazide, but it has limited data for the recommendation. Cox et al, conducted a trial to compare the combination of diuretic strategies, 5mg oral metolazone twice daily vs 500 mg IV chlorothiazide twice daily vs 30mg tolvaptan daily, concomitantly with high-dose IV furosemide. This study showed that, tolvaptan has similar results in term of weight loss with other diuretic, but only tolvaptan was associated with an improved urine output-based diuretic efficiency, and smaller decreases in serum sodium and chloride compared to others.[34]

Renal Properties

Patients that require more diuretic agents are linked to worsening renal function (WRF), this finding makes researchers conduct some study. Although the impact of renal function during ADHF is less defined, there have been some studies conducted to clear things up. A RCT conducted by Kimura et al, which compared addition of early tolvaptan administering (24 hours) to fixed furosemide dose (20mg/day) with furosemide that dosed up to 30mg/day, had significantly WRF and natrium serum level. A kaplan-meier analysis for survival free of cardiac death, or readmission for heart failure during the 90 days after discharge was done. Event free rate was significantly lower in the persistent WRF (p-WRF) subgroup, and the incidence of p-WRF was significantly lower in the tolvaptan group.[35]

This renoprotective benefit of tolvaptan as add-on therapy is also observed by Yamamoto et al, in their retrospective study. Changes in serum creatinine (Cr) was significantly increased in the non-tolvaptan group (+0.2 mg/dL vs -0.1 mg/dL), and the changes of GFR was significantly decreased in non-tolvaptan group (-2.7 mL/min/1.73m2 vs +1.4 mL/min/1.73m2). The WRF rate in the tolvaptan group was significantly lower (2.5% vs 15.4%) especially in the heart failure with preserved ejection fraction (HFpEF) patients. When multiple logistic regression performed for analyzing the predictors of WRF, tolvaptan also found to be an independent factor for reducing WRF (OR: 0.14 [0.02-0.98]).[36] These similar results also found by Kin et al, tolvaptan add-on therapy had lower incidence of WRF (8.5% vs 24%), and tolvaptan add-on therapy was an independent factor of preventing WRF.[37] But these results were varied, Felker et al in his study showed that WRF was more frequent in tolvaptan arm than in placebo arm (39% vs 27%).[31]

Wang C, et al showed in their meta-analysis that Tolvaptan decreased the rate of WRF compared with furosemide. Tolvaptan could also elevate the sodium level as fast as 2 days, indicating that tolvaptan was more suitable for ADHF with hyponatremia.[38]

Long-term Effect

Konstam *et al.* conducted a trial that included patients aged 18 years or older with reduced left ventricular ejection fraction, NYHA III/IV symptoms, and hospitalization caused by ADHF. The patients were randomized to receive a placebo or 30 mg/day Tolvaptan (standard therapy was given to both groups). In the short term, when added to standard therapy, Tolvaptan showed improved signs and symptoms of ADHF with no severe adverse reactions.[39] In the long term, Tolvaptan was non-inferior for mortality compared to standard therapy (Kaplan Meier analysis for mortality is 25% in the Tolvaptan group and 26% in the placebo group, and death

from cardiovascular causes or first hospitalization is 42% and 40.2%, respectively). [40] Wang C *et al.* also showed that tolvaptan was not inferior in mortality and prevented rehospitalization compared to conventional therapy, but a subgroup analysis showed that more than 15mg/day of Tolvaptan had the highest probability of achieving the best efficacy in preventing mortality and rehospitalization.[41]

However in Asian population, Nakao et al. in his meta-analysis showed that, compared to the conventional therapy Tolvaptan as add-on therapy did not show to improve long-term mortality and HF readmission in Japanese patients with HF. (OR: 1.02 [0.69 – 1.52], and OR: 0.73 [0.24 – 2.22] respectively). [42]

Cardiac remodeling prevention is one of the hypotheses that encourages the possible beneficial use of Tolvaptan. Udelson *et al.* conducted an RCT to examine the effects of Tolvaptan on changes in the left ventricular volume over time. There were no significant changes in the left ventricular end-diastolic volume (LVEDV) after one year of observation.[43] However, since this study was only conducted in stable HF patients, more studies are needed to confirm the cardiac remodeling effect of vaptans in patients after hospitalization due to ADHF.

Cost Effectiveness

Cost is one of the topics currently being considered and studied thoroughly. Dasta *et al.* conducted a study in 2018 that analyzed data from the Hyponatremia Registry (HNR), a multicenter and global observational study of management of hospitalized patients with euvolemic or hypovolemic hyponatremia. Seven hundred sixty-two patients, who were hospitalized because of heart failure, were analyzed. The data showed that patients administered with tolvaptan had a shorter hospitalization duration than patients with water restriction only (4 vs 6 days). Additionally, the average cost of 15 mg and 30 mg was compared with the average cost of hospitalization per day in the United States. Tolvaptan use was estimated to be 2295 USD cheaper than only water restriction regimen. However, the weakness of this study was only relying on data taken from HNR, which might present with input errors. Furthermore, the sample characteristics cannot be determined as in an experimental study. The cost of hospitalization is different in each country; therefore, this research cannot be used as an international reference.[44]

General Usage of Vaptans

Tolvaptan is used once daily orally with flexible titration. The starting dose is 15 mg/day and can be titrated to 30 mg/day after at least 24 hours and up to 60mg/day. During the initiation and titration, clinicians should frequently monitor the electrolytes and volume. Tolvaptan is contraindicated in patients with hypovolemic hyponatremia, anuria, hypersensitivity, concomitant use of potent CYP3A inhibitors, urgent need to raise serum sodium acutely, and inability to respond to thirst. Chronic use of tolvaptan can cause liver injury; thus, tolvaptan should not be given for more than 30 days to minimize the risks. Patients with cirrhosis should be monitored carefully as GI bleeding may occur.[45]

VRA use has been mentioned before in the 2013 ACCF/AHA guidelines for patients hospitalized with volume overload and severe hyponatremia and with a IIb class of recommendation and a B level of evidence.[6] On the other hand, the 2016 ESC guidelines also stated that VRA, such as Tolvaptan, can treat patients with volume overload and resistant hyponatremia, but did not state the class of recommendation nor the level of evidence.[3] These guidelines should be updated because newer evidence showed that FDA-approved vaptan such as Tolvaptan could be used as an adjuvant therapy to standard therapy (loop diuretic and/or MRA) to lower the use of more loop diuretics. This is important because higher doses of loop diuretics may worsen the renal function, and the addition of VRA provides better relief of congestive symptoms and stable serum sodium levels. VRA can still be used in patients with ADHF without hyponatremia, but ADHF patients with hyponatremia may get the most benefit.[30,35,41,46]

Risks

The use of vasopressin receptor antagonists can cause some side effects, such as thirst,

pollakiuria, and dry mouth. Thirst is found in 29% of patients and may become a problem if the patients increase their fluid intake.[44] In the administration of Conivaptan, 9.8% of patients experienced a rapid correction of serum sodium (>12 mEq/l/day) with no neurological symptom drawbacks especially the central pontine myelinolysis (CPM).[48]

Tolvaptan use is safe and only has some minor adverse reactions. An RCT found that 39.2% of patients complained of thirstiness, but these side effects were not prominent if the drugs were only given for 7-14 days. Other studies also reported that thirst was only felt mostly during the first three days.[49,50] Some case reports demonstrated that tolvaptan use in the elderly may cause liver damage.[51] The risk of liver damage in patients with ADPKD is well known. In an RCT of 961 patients, 1.5% of patients stopped the drug due to liver dysfunction, 4% of patients had a significant improvement in liver function, and 0.9% of patients had an increase in bilirubin.[52] However, no studies have reported liver damage in patients with AHF, especially ADHF.

A retrospective study by Fujioka et al found that although the continuous use of tolvaptan after discharge did not affect mid-term cardiac events of HF overall, it may be associated with increased cardiac events in the subgroup with preserved renal function. The exact cause was not determined, but the author argued that thirst, a side effect of Tolvaptan, might have increased water intake after discharge. This result suggested that the use of Tolvaptan might need to be limited to in-hospital management of ADHF.[53]

In laboratory animals, Conivaptan exerted fetopathic effects at doses that were less than the therapeutic dose. This delayed labor in rats at doses that were equivalent to their therapeutic doses. Thus, Conivaptan has been considered in Pregnancy Category C by the FDA. Another thing to consider is that the administration of Conivaptan can increase plasma concentrations of midazolam, simvastatin, digoxin, and amlodipine. Conivaptan is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), leading to serious drug-drug interactions. Tolvaptan has less potential for drug-drug interactions. Coadministration of Conivaptan with potent inhibitors of (CYP3A4), such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated. Due to this drawback, an oral preparation of Conivaptan has not been developed.[47]

There have been efforts to develop novel vasopressin antagonists, one of which is the highly V2 selective Lixivaptan. The BALANCE trial, an RCT designed to evaluate the effect of Lixivaptan in ADHF, reported a statistically significant but modest increase in sodium concentration. However, there was an unusually high number of deaths early in the Lixivaptan group for unclear reasons – 15 patients in the first ten days of treatment versus four in the placebo group. This raised concerns about the safety of Lixivaptan use in patients hospitalized with ADHF. Thus, on September 13, 2012, the FDA voted unanimously against recommending Lixivaptan for the treatment of hypervolemic hyponatremia.[54]

CONCLUSION

The use of aquaretics in patients with heart failure is well known in scientific writing, but this has only focused on the short-term, long-term, and the safety of their use. The use of aquaretics, especially tolvaptan, with a starting dose from 15 mg/day titrated up to 60mg/day may lead to good outcomes as adjuvant therapy in reducing symptoms from congestion such as shortness of breath, and objective parameters such as weight reduction, and in correcting hyponatremia. This use of the drug is non-inferior in terms of mortality compared to standard therapy. Clinicians need to investigate more on aquaretics to provide the best therapy for ADHF patients.

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