Vasopressin Receptor Antagonists (Vaptans) in Heart Failure

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Abstract

Vasopressin receptor blockade is an interesting therapeutic target in patients with heart failure. To date, however, clinical trials of vasopressin antagonists have failed to demonstrate any significant benefits in terms of long-term mortality or heart failure–related morbidity. Limited short-term beneficial clinical effects reported in patients with acute heart failure, volume overload and resistant hyponatraemia translate into only a limited role of vaptans in recommended management of this patient population.

Keywords: heart failure; hyponatraemia; tolvaptan, vasopressin antagonists, vaptans

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Introduction

Hyponatraemia is a relatively prevalent laboratory finding in HF – it has been observed in almost one in every five patients hospitalized with new-onset or worsening HF.[1] Importantly, in this population hyponatraemia has been shown to be associated with longer hospital stays as well as higher in-hospital and long-term mortality.[2] Arginine vasopressin is a peptide neuroendocrine hormone, increased levels of which are found in patients with HF.[3] Acting through 3 subtypes of receptors, it causes vasoconstriction and cardiac remodeling (receptors V₁a), adrenocorticotropic hormone release (receptors V₁b) and water reabsorption (receptors V₂), thus increasing preload and afterload.

Differences between vasopressin-receptor antagonists

Vasopressin-receptor antagonists (vaptans), which induce hypotonic diuresis and are aimed at the treatment of hyponatraemia, have been proposed as a therapeutic option for patients with HF.[4] Three of these agents have been more extensively studied in this clinical scenario, namely: tolvaptan, conivaptan and lixivaptan (table 1). However, only tolvaptan and conivaptan have been approved for clinical use in hyponatraemia (in the USA). Lixivaptan, following the FDA’s rejection of approval for treatment of hyponatraemia, is now repurposed and being developed for the treatment of autosomal dominant polycystic kidney disease.

Evidence from clinical trials

The largest study on the use of tolvaptan in HF patients was the EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan). The authors of this prospective, multicentre, randomized, double-blind, placebo-controlled study assessed the short- and long-term efficacy and safety of tolvaptan added to optimal treatment in over 4100 patients hospitalized with an exacerbation of chronic HF with reduced LVEF. They observed no effect on long-term mortality or HF-related morbidity,[6], but during short-term follow-up there was a greater weight loss accompanied by an attenuation in many signs and symptoms of HF, including dyspnoea and oedema. Importantly, there was no excess of serious adverse events, including renal failure and hypotension in an active treatment arm.[7] Similar observations regarding the short-term efficacy of adding tolvaptan for relieving dyspnoea have also been demonstrated in acute HF patients with diminished renal function in the AQUAMARINE study (Answering the Question of Tolvaptan’s Efficacy for Patients With Acute Decompensated Heart Failure and Renal Failure).[8] In contrast, the more recent, but much smaller (257 patients) TACTICS-HF trial (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) - has shown that administration of tolvaptan in patients hospitalized due to acute HF and congestion resulted in an increased reduction in body weight and the greater net fluid loss, but with no difference in dyspnoea relief,
Table 1. Characteristics of the most extensively studied vasopressin-receptor antagonists[5].

<table>
<thead>
<tr>
<th></th>
<th>Conivaptan</th>
<th>Tolvaptan</th>
<th>Lixivaptan</th>
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</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>non-selective V1a and V2 antagonist</td>
<td>selective V2 antagonist</td>
<td>selective V2 antagonist</td>
</tr>
<tr>
<td>Route of administration</td>
<td>intravenous</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>Dosing</td>
<td>20-40 mg/d</td>
<td>15-60 mg/d</td>
<td>10-400mg/d</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>3-8 hours</td>
<td>6-8 hours</td>
<td>7-10 hours</td>
</tr>
</tbody>
</table>

or in-hospital or post-discharge clinical outcomes.[9] Moreover, tolvaptan-treated patients were more likely to experience worsening renal function.

Importantly, tolvaptan has been shown to be effective in increasing serum sodium concentrations in patients with hyponatraemia, both in cases of acute and chronic HF.[10,11] The most common side effects associated with tolvaptan administration, described consistently in the literature, have included thirst, dry mouth and increased urination.

There are fewer data available on the use of conivaptan in patients with HF, compared to tolvaptan. In a study comprising 142 patients with symptomatic HF, the administration of conivaptan led to increased urine output and a decrease in pulmonary capillary wedge pressure and right atrial pressure, with no significant changes in blood pressure and heart rate.[12] This improvement in urine output without affecting vital signs has been confirmed in another later study.[13]

Vasopressin receptor antagonists have also been studied in the setting of decompensated right-sided HF. Vidic et al. in a retrospective observational study including patients hospitalized with clinical and echocardiographic evidence of right-sided HF have shown that the use of vaptans (90% of patients received tolvaptan and the remaining 10% were treated with conivaptan) was associated with a significant increase in urine output and serum sodium with a decrease or stabilization of diuretic dosing in the early treatment period.[14] The authors concluded that vaptans may be useful in patients failing conventional diuretic-based treatment, although being an observational study an effect of selection bias cannot be excluded.

Vasopressin-receptor antagonists in the European Society of Cardiology guidelines on heart failure

In the most recent 2016 European HF guidelines, vaptans receive relatively little discussion, and only a limited recommendation for patients with HF, with the statement that “Tolvaptan may be used to treat patients with volume overload and resistant hyponatraemia” based on the EVEREST trial.[15]

Conclusions

Due to a relatively high prevalence of hyponatraemia in HF patients and the role of vasopressin in this electrolyte and volaemia abnormality, as well as the influence of hyponatraemia and increased levels of vasopressin itself on worse clinical outcomes in this population, the vasopressin receptors blockade seems to be an appealing therapeutic target. However, currently available data suggest no influence of vasopressin receptor antagonists (vaptans) on long-term mortality or HF-related morbidity. Limited short-term beneficial clinical effects described in patients with acute HF with volume overload and resistant hyponatraemia mean that this interesting class of agents play only a minor role in our management of the population burden of HF.

Declarations of interest

The authors declare no conflict of interest.

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