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Review

Arginine vasopressin antagonism in heart failure: Current status and possible new directions

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ABSTRACT

Modulating neurohormonal imbalance is the cornerstone of successful therapy in patients with chronic heart failure with reduced ejection fraction (HFrEF). Plasma arginine vasopressin (AVP) levels are elevated in HFrEF and may contribute to disease progression by excess signaling at either the V1a or V2 receptors. The effects of V1a receptor antagonism are almost completely unexplored, but V1a signaling is closely related to that for angiotensin II and blocking that receptor deserves further study. Interfering with V2 signaling causes free water diuresis and improves congestion without worsening renal function when added to loop diuretics but alone did not improve outcomes when carried into the post-acute phase in one large study. Outcomes in chronic HFrEF are quite good while outcomes in acute HF remain poor. Therefore, further study of V2 or combined V1/V2 blockade of the effects of AVP would most likely yield positive results in patients with acute HF, perhaps especially as alternative, not adjunctive therapy to loop diuretics.

Contents

Introduction

Decades have passed since the first reports of elevated plasma arginine vasopressin (AVP) levels in patients with heart failure (HF). The first report was by the Japanese investigator Yamane using a bioassay [1], and was later confirmed by several centers in the USA when more powerful and reliable radioimmunoassays became available [2,3]. While the earliest report from Japan [1] included patients with many forms of HF, the subsequent reports focused on patients with acute HF and hyponatremia [2] and later chronic HF with or without hyponatremia [3]. Few data have been reported in patients with HF with preserved ejection fraction (HFpEF).

It has also been decades since the suggestions were made that antagonizing the effects of AVP might be useful in patients with HF apart from treating hyponatremia [4]. There are two major receptors of relevance to HF for AVP, the V1a and the V2 receptors. Over the past two decades we have had extensive experience with blocking the V2 receptor, largely but not exclusively in patients with HF with reduced ejection fraction (HFrEF). Only very limited data are available concerning blocking the V1a receptor, and only

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in HFrEF since it has been difficult to develop orally effective antagonists to this receptor. Only one report of any size exists with blocking both receptors in acute HF, using the only available intravenous antagonist to both receptors. In this brief review I shall summarize the current rationale for blocking the receptors for AVP primarily in patients with HFrEF and primarily in acute HF, summarize the data we currently have, and suggest avenues for future study.(Fig. 1).

Rationale for blocking the V1a and V2 receptors in HFrEF

The basis for assuming that blockade of these receptors would be useful in HFrEF rests on the known power of exploiting neurohormonal imbalance in this syndrome. All of the pharmacologic treatments which have improved survival in HFrEF are based on antagonizing the effects of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), and more recently, enhancing signaling from beneficial peptides such as the natriuretic peptide family as shown by the superiority of valsartan/sacubitril over angiotensin-converting enzyme inhibition [5]. Along with plasma norepinephrine, renin, and atrial natriuretic peptide, AVP was described in the original report which postulated the possible pathophysiologic role of neurohormonal imbalance in HFrEF [6]. It is worth noting that at the time this theory was largely dismissed, since it was thought that increased levels of these 'neurohormones' were more likely epiphenomena rather than being actively involved in the pathophysiology of the syndrome.

The rationale for blocking the V1a receptor is based on the intracellular signaling pathways that are engaged when this receptor is activated. These are nearly identical to those activated by the AT1 receptor for angiotensin II. The result of each is increased intracellular calcium, resulting in vasoconstriction in smooth muscle, and increased protein synthesis in myocardial cells. This can lead to vasoconstriction and inappropriate myocardial hypertrophy, both of which can contribute to ventricular remodeling and progressive HF by load-dependent and load-independent mechanisms. We know this can happen due to chronically enhanced signaling within the RAAS since blocking the ATI receptor and/or lowering angiotensin II levels improves survival in HF. There is no reason whatever to suspect that a similar effect from blocking the V1a receptor could not occur. As noted above, we know that AVP levels are increased in HFrEF, and using hemodynamic studies as a surrogate for long term non-hemodynamic effects (as was the case with early studies using RAAS blockers) there is definitely the possibility that blocking the V1a receptor could be useful [7,8]. With the RAAS blocked, it is even possible that V1a signaling could be more important, but we lack data in patients on RAAS blockers. We have no long-term data with V1a antagonism in HF because we have not, at least until now, had a drug that could safely and effectively perform this function.

The rationale for blocking the V2 receptor other than for treating hyponatremia is two-fold. First, since this receptor governs free-water retention in the renal tubules, blocking the receptor could produce a free-water diuresis, which in fact it does in HF as many studies have shown. This effect could in general be useful to help with fluid balance in HF, but alone is not adequate to change outcomes as shown by the long-term phase of the EVEREST study [9]. When hyponatremia is present, however, blocking this receptor is highly effective in restoring serum sodium to normal. In the USA, blocking this receptor is the only therapy recognized by the Food and Drug Administration to be safe and effective for treating dilutional hyponatremia, including that seen in HF. Whether this would change outcomes in hyponatremic HF patients is not known, although a retrospective analysis of the hyponatremic population in EVEREST suggests that it might [10].

The other rationale for blocking the V2 receptor in HFrEF is more subtle, and rests on the possibility that this approach might be as effective but safer as a decongestive strategy especially in patients with acute HF [11]. The cornerstone of treatment of acute HF is loop diuretics, and outcomes remain extremely poor in acute HF. Loop diuretics by their intrinsic mechanism of action stimulate the RAAS as well as the sympathetic nervous system and vasopressin release, and acutely this is associated with adverse hemodynamic and renal effects [12,13]. It is possible that the intense neurohormonal stimulation from loop diuretics at a time when patients are already quite vulnerable due to intense congestion, unstable renal function, and hemodynamic compromise could be harmful, despite effecting some diuresis. V2 antagonists do not stimulate neurohormonal activation and do not adversely affect renal function. There are two short-term studies, one in acute and the other in chronic HF, which showed that replacement of loop diuretics with a V2 antagonist produced comparable clinical benefit but a much preferable effect on renal function and neurohormonal balance [14,15]. These results are intriguing and suggest the need for further exploration of V2 antagonism as an alternative approach to loop diuretics in HF, at least in patients with HFrEF although the study in acute HF included some HFpEF patients as well.

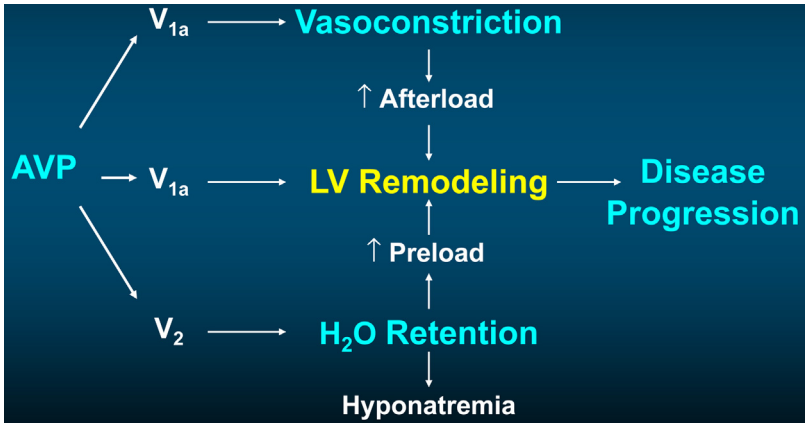

Fig. 1. AVP and Congestive Heart failure Pathophysiology. AVP could contribute to the pathophysiology of congestive heart failure by several mechanisms. V1a receptor activation increases intracellular calcium in smooth muscle and myocardial cells. The result is an increase in vascular tone which could contribute to increased afterload, and direct stimulation of myocardial cell growth which could contribute to inappropriate hypertrophy. Both mechanisms could contribute to ventricular remodeling and failure. V2 activation increases free-water retention in the renal tubules, and could thereby contribute to volume expansion, diastolic wall stress, edema, and hyponatremia. AVP, arginine vasopressin; LV, left ventricular.

Given the strong rationale for blocking the V1a and V2 receptors individually, it makes sense to block them together if possible. This would be 'comprehensive' blockade of the effects of AVP and if added to the interventions already known to be successful with the RAAS, sympathetic nervous system, and natriuretic peptide family be the 'next step' in neurohormonal modulation in HF, a path which thus far has been a near-infallible guide to success in treating this syndrome. The other reason to prefer combined blockade is to prevent unwanted excessive signaling at the unblocked receptor if plasma AVP levels increase in response to blockade of either receptor alone. This could happen by displacing hormone from binding sites in response to V1a blockade which could cause unwanted free-water retention. In response to selective V2 blockade, plasma AVP does increase due to the increase in osmolality and that could lead to unwanted V1a effects. Plasma AVP levels rose in the active treatment arm of EVEREST and correlated with mortality, an effect which has been speculated to have offset any potential benefit of long-term V2 antagonism [16].

Current status of AVP antagonism in HF

A comprehensive review of the clinical trials experience of AVP antagonism in HF is beyond the scope of this brief review. What we know is the following: First, adding a V2 antagonist to standard therapy in acute HF consistently produces incremental weight loss and net fluid loss, with improvement in dyspnea. This has been seen in ACTIV [17], EVEREST [9], TACTICS [18], and SECRET [19], all of which were randomized double-blind trials, and as well in AQUAMARINE [20], a randomized but not placebo-controlled trial conducted in Japan. It should be noted that the precise endpoints and timing of endpoints varied considerably among these trials, so some are considered to be 'positive' and some 'negative' depending on the nature of the endpoints, but every one of the studies did demonstrate positive effects on fluid balance and dyspnea, at some time point, relative to placebo or control patients. Also, and importantly, the increased decongestive effect came without any worsening of renal function as reflected in serum creatinine (Cr), other than on one day of serum Cr measurements in the TACTICS trial [the effects on renal function in EVEREST were more complicated as there was a tendency for small increases in Cr but lower blood urea nitrogen (BUN) such that the BUN/Cr ratio was in fact favorable vs loop diuretic alone]. Thus, as adjunctive therapy in acute HF, V2 antagonism has predictable, measurable, and beneficial clinical effects. Among these trials, only EVEREST had a chronic phase, and while the decongestive effects without prejudice to renal function were seen over the long term, no outcomes benefits were observed. Unless as noted above there was an offsetting effect from unwanted V1a stimulation, it is not likely that pure V2 antagonism as adjunctive therapy itself produces long-term clinical benefit.

Second, we have one clinical trial of combined V1a and V2 antagonism in acute HF [21]. This was a placebo-controlled randomized study and the results were similar to those with pure V2 antagonism. Importantly, there was no hypotension or adverse renal effect from adding the V1 antagonist to the V2. This trial opens the door to additional study of combined antagonism in acute HF. No chronic experience of any size exists to draw conclusions at this point regarding long-term benefit of combined antagonism.

Future directions

Based on what we now know, future studies of vasopressin antagonism should probably focus largely on such therapy as an alternative to loop diuretic use in acute HF, with either a pure V2 antagonist or a combined antagonist, and both as adjunctive and alternative therapy in chronic HF using a combined antagonist. The effects of pure V2 antagonism as adjunctive therapy in acute and chronic HF are sufficiently well-characterized that no further studies of this nature are warranted. However, the intriguing results of preliminary studies of this therapy as an alternative to loop diuretics in acute and chronic HF, combined with the demonstrated power of manipulating neurohormonal imbalance, the exceedingly poor outcomes in acute HF, and the possibility that the adverse effects of massive loop diuretic use could be contributing to these outcomes, makes further study of the effects of pure V2 antagonism as an alternative decongestive strategy in acute HF potentially very intriguing. It would also be reasonable to carry such a study into the post-acute phase as well.

If additional study of a V2 antagonists as alternative therapy in acute HF makes sense, adding a V1a antagonist could further enhance benefit–particularly if extended into the chronic phase post-discharge since any benefits of V1a blockade by analogy with other interventions such as those with the RAAS take time to become apparent. It is unlikely that loop diuretics could be eliminated entirely long term, but if they were reduced substantially by using a V2 antagonist as an alternative, while adding V1-blockade to the mix, it is quite possible that an EVEREST-like study could show long-term benefit with a combined antagonist. An ideal strategy would be to design a 3-arm version of EVEREST using a balanced antagonist instead of a pure V2 antagonist. One arm would be standard therapy with as much loop diuretic as needed, a second would be a loop diuretic + adjunctive therapy with a balanced antagonist, and the third would be a no-loop-diuretic arm. Such a study may be within our capabilities soon since a new and potentially promising orally effective combined antagonist now is available for clinical investigation [22].

Conclusion

The rationale for vasopressin antagonism in HF is as strong or stronger now than it was nearly four decades ago when the first radioimmunoassay-based reports of increased AVP levels in patients with HF were published. In stable chronic HF, the sample size needed to show any benefit of a combined antagonist would be large in view of the results with valsartan/sabubitril. Which is why, perhaps, the best next steps with any new agents should focus on the population currently of greatest need of improved outcomes, i.e. acute HF. Here, the extensive experience with adjunctive therapy with pure V2 antagonists has established their clinical profile, and further study of this therapy as an alternative to loop diuretics could represent an exciting new approach to decongesting these patients given persistent poor outcomes and in face of what is known about the neurohormonal and renal differences between V2 antagonists and loop diuretics. Adding a V1a antagonist to a V2 antagonist makes even more sense in acute HF, and having a balanced antagonist either as adjunctive or alternative therapy to loop diuretics would further define the long-term utility of V1a blockade in chronic HF. And finally, since most of the rationale for AVP antagonism in HF rests on the success of other neurohormonally-based treatments in HFrEF, it would probably make sense to focus on HFrEF patients since HFpEF is a heterogeneous syndrome in which the role of neurohormonal imbalance in disease progression is almost completely unexplored.

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References

[1] Yamane Y, Plasma ADH. level in patients with chronic congestive heart failure. Jpn Circ J 1968;32:745–59.
[2] Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med 1981;305:263–6.
[3] Goldsmith SR, Francis GS, Cowley Jr AW, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1983;1:1385–90.
[4] Goldsmith SR. Vasopressin: a therapeutic target in congestive heart failure? J Card Fail 1999;5:347–56.
[5] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
[6] Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984;101:370–7.
[7] Creager MA, Faxon DP, Cutler SS, Kohlmann O, Ryan TJ, Gavras H. Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. J Am Coll Cardiol 1986;7:758–65.
[8] Goldsmith SR, Francis GS, Cowley Jr AW, Goldenberg IF, Cohn JN. Hemodynamic effects of infused arginine vasopressin in congestive heart failure. J Am Coll Cardiol 1986;8:779–83.
[9] Konstam MA, Gheorghiade M, Burnett Jr JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–31.
[10] Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail 2013;19:390–7.
[11] Goldsmith SR, Bart BA, Burnett J. Decongestive therapy and renal function in acute heart failure: time for a new approach? Circ Heart Fail 2014;7:531–5.
[12] Francis GS, Olivari MT, Goldsmith SR, Levine TB, Pierpont G, Cohn JN. The acute response of plasma norepinephrine, renin activity, and arginine vasopressin to short-term nitroprusside and nitroprusside withdrawal in patients with congestive heart failure. Am Heart J 1983;106:1315–20.
[13] Costello-Boerrigter LC, Smith WB, Boerrigter G, Ouyang J, Zimmer CA, Orlandi C, et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. Am J Physiol Renal Physiol 2006;290:F273–8.
[14] Jujo K, Saito K, Ishida I, Furuki Y, Kim A, Suzuki Y, et al. Randomized pilot trial comparing tolvaptan with furosemide on renal and neurohumoral effects in acute heart failure. ESC Heart Fail 2016;3:177–88.
[15] Udelson JE, Bilsker M, Hauptman PJ, Sequeira R, Thomas I, O'Brien T, et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. J Card Fail 2011;17:973–81.
[16] Lanfear DE, Sabbah HN, Goldsmith SR, Greene SJ, Ambrosy AP, Fought AJ, et al. Association of arginine vasopressin levels with outcomes and the effect of V2 blockade in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST Trial. Circ Heart Fail 2012;6:47–52.
[17] Gheorghiade M, Gattis WA, O'connor CM, Adams Jr KF, Elkayam U, Barbagelata A, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291:1963–71.
[18] Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. J Am Coll Cardiol 2017;69:1399–406.
[19] Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol 2017;69:1409–19.
[20] Matsue Y, Suzuki M, Torii S, Yamaguchi S, Fukamizu S, Ono Y, et al. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. J Card Fail 2016;22:423–32.
[21] Goldsmith SR, Elkayam U, Haught WH, Barve A, He W. Efficacy and safety of the vasopressin V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure: a dose-ranging pilot study. J Card Fail 2008;14:641–7.
[22] Kolkhof P, Tinel H, Buchmueller A, Pook E, Wasnaire P, Schmeck C, et al. Get the right balance: a novel vasopressin receptor antagonist equally blocks human V1a and V2 receptors and inhibits the release of plasminogen activator inhibitor-1 from cardiomyocytes. Eur Heart J 2016;37:620 (Abstract).