Editorial

Vasopressin antagonists in CHF: ready for clinical trials?

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Received 28 January 2002; accepted 28 January 2002

See article by Naitoh et al. [7] (pages 51–57) in this issue.

Improving survival in congestive heart failure is currently based on blunting the effects of inappropriately increased adrenergic drive, as well as of increased circulating and tissue levels of angiotensin II and aldosterone [1–5]. The sympathetic nervous system and renin–angiotensin system comprise two of the three components of the ‘neurohumoral axis’ originally proposed as links to the fundamental pathophysiology of heart failure in 1984 [6]. The third component of that axis as originally postulated was arginine vasopressin (AVP). Research into the possible role of AVP in heart failure has been hampered until comparatively recently by the absence of appropriate antagonists. Now, however, highly effective antagonists of the V1a and V2 receptors for AVP are available, and at least in preliminary human studies, are safe and well tolerated. The study by Naitoh in the current issue of Cardiovascular Research [7] should stimulate considerable interest in further human work with these compounds.

The decision to target a ‘neurohumoral’ or other substance in heart failure should be based on a sound pathobiological rationale, coupled with evidence that enough of the substance in question is present to produce an adverse effect. Then one needs to perform convincing pre-clinical studies, and initially, human studies in which appropriate measurements are made in small series of subjects. Only then can or should larger outcomes studies be undertaken. What constitutes convincing preliminary evidence is, however, controversial. Traditionally, improving hemodynamic measurements or showing a beneficial effect on exercise capacity were viewed as important. Unfortunately, angiotensin converting enzyme inhibitors, aldosterone antagonists, and beta adrenergic blockers have little or no positive short term effect on hemodynamics or exercise, yet produce significant benefits on major outcomes such as survival and hospitalization [1–5]. Other interventions including powerful vasodilators and inodilators that exert positive effects on hemodynamics and exercise, adversely affect survival [8–10]. At this point there is therefore no universally agreed upon surrogate measure for the evaluation of new therapy in heart failure, but most investigators would probably agree that a reduction in left ventricular volume or mass, coupled with a fall in plasma levels of ANP or BNP (reflecting both reduced wall stress and a de-induction of fetal gene programs associated with maladaptive hypertrophy) are as close to meaningful surrogates as we have.

AVP is a desirable candidate for neurohumoral targeting in CHF for several reasons. Firstly, through the V1a receptor it is capable of producing significant vasoconstriction, thereby increasing afterload stress on the left ventricle [11]. Secondly, again though the V1a receptor, AVP directly stimulates protein synthesis within the myocyte, an effect sharing similar intracellular pathways as angiotensin II [12,13]. Under conditions of reduced AII, V1a-mediated signaling could theoretically assume greater relative and/or absolute importance. Thirdly, again via the V1a receptor, AVP could cause significant coronary vasoconstriction, leading to ischemia. Fourthly, via the V2 receptor AVP could alter serum sodium concentration and contribute to volume expansion and increased ventricular preload. AVP is therefore capable of contributing to increased ventricular wall stress as well as inappropriate cellular hypertrophy by several direct and indirect mechanisms.

The pathophysiologic rationale for AVP antagonism is therefore clear. Is there enough AVP mediated signaling to justify attempts to interfere with it? Most preliminary evidence would suggest an affirmative answer. AVP levels are increased in heart failure and after myocardial infarction [14–18]. One study showed a correlation with outcomes and AVP in patients with postinfarction LV dysfunction [19]. Acutely, infusing AVP produces adverse hemodynamic effects in chronic heart failure, while antagonizing the V1a receptor produces hemodynamic benefit [20,21]. The latter effect has been seen in humans as well as several animal models of CHF [22,23]. Combined V1a...
and V2 antagonism also produces acute hemodynamic benefit in experimental and human heart failure [24–27]. Long term, V2 receptor antagonism produces sustained aquaresis, without measurable hemodynamic benefit [28], but has not been investigated with concomitant standard therapy. These studies taken together suggest that at least as reflected by hemodynamics and water retention, the plasma AVP levels seen in heart failure or post MI produce clinically relevant effects. These studies of course do not address outcomes, nor have they incorporated more sophisticated surrogate measures of the sort we now would like to see.

The current study of Naitoh et al. is of major importance because it is the first long term study of a combined V1a and V2 antagonist (conivaptan), utilizes a well accepted model of post infarction remodeling, incorporates at least one of the critical cotherapies required in the clinical setting the study is designed to model, and includes important structural and humoral markers. The study is significantly positive in several respects.

Conivaptan alone decreased RV mass, but not arterial pressure, ANP levels or LV mass. Conivaptan combined with captopril, however, decreased arterial pressure, RV and LV mass to a greater degree than was seen with captopril, and moreover, decreased ANP levels. These results suggest that while combined V1a and V2 antagonism alone is insufficient to blunt left ventricular remodeling, probably because of unopposed stimulation of the renin–angiotensin–aldosterone axis and sympathetic nervous system, the combination of ACEI and AVP antagonism has greater effects than either treatment alone on both direct (mass) and indirect (ANP) measures of cardiac remodeling. As such, the combination certainly would hold promise for similar investigation in humans.

Of course, since conivaptan is a mixed antagonist, one can not reliably distinguish V1a from V2 effects. The distinction is important, since if the effect is primarily V2 mediated, it is not clear that the overall benefit is distinct from what might be produced by conventional diuretics or nitrates. Further preclinical work with pure V1a antagonism in the same setting, or comparisons with V2 antagonists and diuretics, would help sort out these concerns.

From a clinical standpoint, the key issues for AVP antagonism relate to which sort of antagonist to use, and in what setting. Pure V2 antagonists might not be of much value in a compensated, non-volume expanded state, although if a diuretic sparing effect could be demonstrated they might prove useful as adjuncts to loop diuretics, lessening adverse stimulation of the renin–angiotensin system and electrolyte imbalance. A pure V2 antagonist might well stimulate unwanted V1a effects, however, if AVP levels rose following administration of competitive antagonists. This was seen in the current study. To prevent this effect, combined antagonism would be most desirable. A selective V1a antagonist would be of potentially the greatest direct myocardial benefit and would not lead to unneeded diuresis, but could lead to water retention if V2 stimulation occurred from increased AVP levels. Pure V1a antagonism like pure V2 antagonism may, therefore, be unwise in a clinical setting over the long term. Adjusting the mix of V1a and V2 antagonism could theoretically be tied to the projected use of a given compound, i.e. more V2 effect for sicker volume expanded patients, more V1a for long term effects in non-volume expanded stable populations.

The setting chosen for investigation of these agents is also crucial. Recent data from an acute human study in stable chronic heart failure with conivaptan revealed normal AVP levels at baseline, and a predominant acute V2 effect [26]. This might not be encouraging for V1a antagonism or combined antagonists in this setting long term. As therapy for CHF improves, it is more difficult to show benefits of new treatment in well-established disease where ‘reverse remodeling’ is difficult to achieve. The most likely setting in which benefit could be demonstrated might therefore be either in very sick patients where both the V1a and V2 signaling might be more important, or as prophylactic therapy after myocardial infarction, with the current experimental study as a guide. In the former setting, clinical endpoints are easier to determine, and in the latter, using MRI determined LV mass and volume, along with plasma BNP or AVP, one could design a relatively small trial, which, if positive using these surrogates, could justify a larger clinical study.

Progressive left ventricular remodeling and congestive heart failure are complex yet lethal phenomena requiring sophisticated management. In the absence of firm knowledge of or the ability to manipulate intracellular and molecular processes governing cell growth, bioenergetics and apoptosis, our therapy must be directed at the known and accessible modulators of these processes in the circulation. Great improvements have been made via interfering with the sympathetic nervous system and the renin–angiotensin–aldosterone system. In my opinion, there is now sufficient rationale and preclinical data to proceed with additional therapy based on interfering with AVP.

References


