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The clinical effects of vasopressin receptor antagonists in heart failure

ABSTRACT

The neurohormone arginine vasopressin (AVP) is a promising target in the treatment of heart failure because AVP promotes congestion and hyponatremia, each of which is associated with poor outcomes. Diuretics are standard therapy for heart failure, but they have several limitations, including worsening renal function and hyponatremia. Blocking AVP leads to effective aquaresis, improvements in hemodynamics and renal function parameters, weight loss, and normalization of serum sodium, without changes in blood pressure or heart rate. In placebo-controlled trials in the inpatient and outpatient setting, the AVP receptor antagonist tolvaptan reduced body weight and edema and normalized serum sodium in patients with heart failure.

KEY POINTS

Arginine vasopressin (AVP) is activated in heart failure. Among its many deleterious effects, elevated levels of AVP lead to congestion and hyponatremia.

Hyponatremia, even when mild, is associated with an increase in mortality in patients with heart failure.

Congestion is responsible for most hospital admissions and readmissions in patients with heart failure.

Antagonists of AVP produce an acute improvement in congestion and hyponatremia. Weight loss and increases in serum sodium with AVP receptor antagonists are sustained.

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OF THE MANY neurohormonal modulators that are activated in heart failure, arginine vasopressin (AVP) is unique in that it promotes water retention, sodium retention, and congestion.[1] An antagonist of AVP may therefore address important problems in heart failure.

The rationale for the use of AVP receptor antagonists in heart failure is threefold. First, congestion is an important target for therapy in patients with heart failure because it represents the leading cause of hospitalization and rehospitalization in this population. Second, diuretic therapy has important limitations. Finally, mild hyponatremia is common and is a major predictor of outcome in patients hospitalized with heart failure.

This article examines in detail this rationale for the role of AVP receptor antagonism in heart failure therapy and reviews available clinical studies of the utility of AVP antagonists in patients with chronic or acute heart failure.

ADMISSIONS AND READMISSIONS ARE FREQUENT

In the United States, a primary diagnosis of heart failure is responsible for 1 million hospital admissions per year, and a primary or secondary diagnosis of heart failure is implicated in 3 million admissions.[2] Even more striking is the postdischarge event rate associated with a heart failure hospitalization: 35% of patients die or are readmitted within 60 days of a hospitalization for heart failure.[2] No other common medical syndrome is associated with such a high mortality and rehospitalization rate.

Approximately 80% of patients hospitalized with heart failure are admitted for worsening chronic heart failure.[2] The main reason for their hospitalization is systemic congestion, as

evidenced by a high rate of dyspnea, rales, and peripheral edema at presentation. Less than 5% have low cardiac output on admission.[2]

Congestion contributes to heart failure progression

Although the primary cause of hospital admissions and readmissions in heart failure patients is congestion, more than 50% of patients have little or no weight loss during hospitalization.[3] What is often not recognized is that hemodynamic congestion, defined as a high left ventricular (LV) filling pressure, may contribute to the progression of heart failure. Among the potential deleterious effects of congestion in heart failure are the following[4]:

- LV remodeling, resulting in increased afterload (wall stress) and worsening mitral regurgitation
- Increased pulmonary artery/renal artery pressure
- Neurohormonal activation
- Subendocardial ischemia and cell death by necrosis and/or apoptosis
- Changes in extracellular matrix structure and function
- Progression of LV dysfunction
- Impaired cardiac drainage from coronary veins (diastolic dysfunction)
- A lower threshold for arrhythmias.

DIURETICS HAVE SEVERAL SHORTCOMINGS

Currently, diuretics are the only therapy in chronic heart failure to reduce fluid overload that results in congestion. Although rapid symptomatic improvement and a decrease in volume overload are observed with diuretic therapy for the acute heart failure syndrome, an alternative to diuretics would be welcome given that diuretic therapy also has several disadvantages. Among these are increased neurohormonal activation, worsening renal function, and electrolyte disturbances.

Hyponatremia as a prognostic predictor

Decreased serum sodium osmolality is one of the electrolyte disturbances caused by diuretic therapy. Even a minor decrease in serum sodium predicts prognosis: in hospitalized patients, each 3-mEq decrease in serum sodium is associated with a 20% increase in mortality within 60 days.[5] These findings were confirmed by the large Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) database (Figure 1), which also revealed that hyponatremia retains its predictive value regardless of whether patients have systolic or diastolic heart failure.[6]

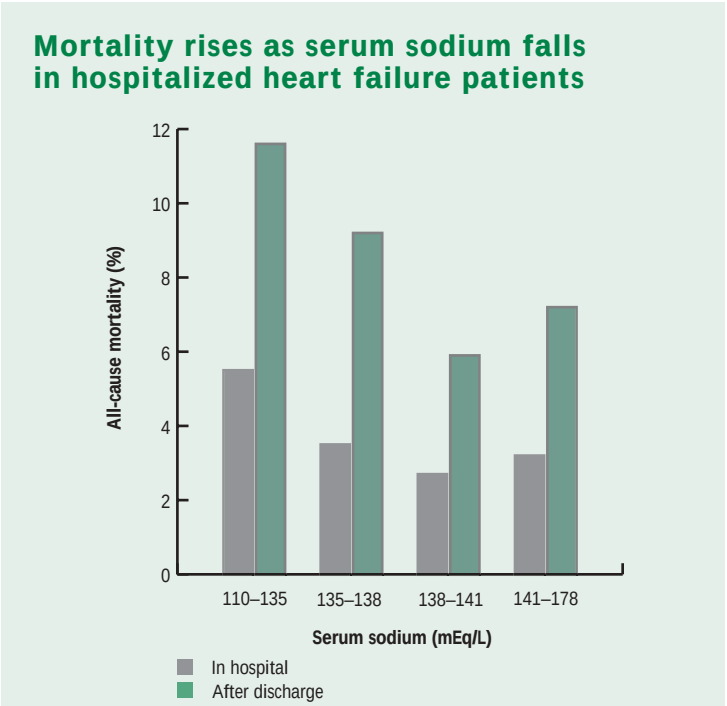

FIGURE 1. The OPTIMIZE-HF database of 48,612 patients hospitalized for heart failure reveals that all-cause mortality, both during the hospitalization and after discharge, increases as serum sodium levels decline. Data from reference 6.

These data are noteworthy because 25% of patients admitted with chronic heart failure have a mild degree of hyponatremia (< 135 mEq/L).[5]

Increasing serum sodium during the hospitalization improves outcomes; an increase in serum sodium of 2 mEq/L or greater is associated with a 14% relative reduction in the risk of mortality at 60 days compared with no change in serum sodium.[7]

BLOCKING AVP

AVP is a nonapeptide hormone synthesized in the hypothalamus. The two distinctive types of AVP receptors are the vasopressin 1 (V_1) and vasopressin 2 (V_2) receptors. The V_1 receptor mediates vasoconstriction and

AVP antagonism exerts favorable hemodynamic effects

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Please see original source figure (figure 2A) in: *Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 2001; 104:2417–2423.*

FIGURE 2. A single intravenous dose of conivaptan 20 mg or 40 mg resulted in an improvement in pulmonary capillary wedge pressure (PCWP) in patients with advanced heart failure.

mitogenesis in the vascular smooth muscle cells; the V_2 receptor mediates the effect of AVP in water excretion. Administration of an AVP receptor antagonist results in aquaresis without activation of plasma neurohormones. The main site of action for the aquaretic effects of AVP receptor antagonists is the V_2 receptor.

Three orally active AVP receptor antagonists have been developed or are under development. Conivaptan is a dual V_1/V_2 receptor antagonist. Tolvaptan and lixivaptan are selective for the V_2 receptor in the principal cells of the renal collecting duct.

To date, two of the AVP receptor antagonists have been studied in human heart failure. Conivaptan has been evaluated in a short-term hemodynamic study, and tolvaptan has been evaluated for acute and longer-term treatment of heart failure in inpatient and outpatient settings.

Favorable hemodynamic changes

Favorable changes in hemodynamics have resulted from AVP receptor antagonism. Udelson et al[8] showed that blocking AVP with the dual V_1/V_2 receptor antagonist conivaptan in patients with advanced heart failure caused a significant decrease in pulmonary capillary wedge pressure (Figure 2) with no significant effect on cardiac index, blood pressure, pulmonary vascular resistance, systemic vascular resistance, or heart rate.

Positive effects on renal physiology

In a direct comparison with the diuretic furosemide in patients with congestive heart failure, the V_2 receptor antagonist tolvaptan increased effective renal plasma flow, renal blood flow, and glomerular filtration rate (GFR).[9] Significant sodium excretion occurs with furosemide but not with tolvaptan administration. These data suggest that furosemide produces negative effects on renal physiology, whereas tolvaptan, acting via a more physiologic mechanism, increases urine production without reductions in renal blood flow and GFR.

Weight loss promotion

In a comparison in patients with heart failure, tolvaptan and furosemide independently contributed to a decrease in body weight at 8 days.[10]

Normalization of serum sodium

In a small, randomized study of patients with hyponatremia (serum sodium < 135 mEq/L), a significant improvement or normalization of serum sodium was observed in the patients assigned to tolvaptan, whereas those randomized to fluid restriction had no significant change in serum sodium levels.[11]

CLINICAL TRIALS IN OUTPATIENTS WITH HEART FAILURE

Tolvaptan was studied in a double-blind, randomized trial of 254 patients with mild systolic or diastolic heart failure who were receiving standard heart failure therapy (ie, diuretic, angiotensin-converting enzyme inhibitor, digoxin, beta-blocker).[12]

After a run-in period, the patients were randomized to 25 days of placebo or one of three doses of tolvaptan (30, 45, or 60 mg/day).

Early and sustained weight loss

At day 1, patients randomized to tolvaptan had decreases in body weight from 0.79 to 0.96 kg from baseline, compared with an increase of 0.32 kg in those assigned to placebo ($P < .001$ for all treatment groups vs place-

bo). The decrease in body weight in patients randomized to tolvaptan was maintained throughout the 25 days.[12]

No change in blood pressure

Unlike other neurohormonal modulators, tolvaptan had no effect on blood pressure.[12] This finding is advantageous because a decrease in blood pressure is one of the most important predictors of a poor outcome in patients hospitalized with acute heart failure [M. Gheorghiade, unpublished pooled data].

Serum sodium change dependent on baseline level

The most common adverse events with tolvaptan in this trial[12] were polyuria, urinary frequency, and thirst. Across the three dose groups, tolvaptan produced a small transient increase in serum sodium, with a differential response according to baseline serum sodium level. Patients with hyponatremia (mean serum sodium < 136 mEq/L) experienced a significant increase in serum sodium starting at day 1, and this increase was maintained throughout the 25-day study period (Figure 3). In contrast, in normonatremic patients (mean baseline serum sodium ≥ 136 mEq/L), serum sodium levels returned to their prerandomization levels following an increase on day 1.

No evidence of remodeling

Tolvaptan had no effect on LV remodeling in another recent double-blind, placebo-controlled outpatient study of 240 subjects with mild to moderate chronic heart failure.[13] No significant changes in ejection fraction or LV end diastolic or LV end systolic volume occurred in response to 30 mg/day of tolvaptan. A post hoc analysis showed that the addition of tolvaptan to standard heart failure therapy reduced mortality and the incidence of worsening heart failure compared with placebo (P = .027), although the effect of therapy on these clinical endpoints was not part of the study design.

CLINICAL TRIAL IN ACUTE HEART FAILURE SYNDROME

The effect of tolvaptan in addition to optimal medical therapy was examined in 319 hospitalized patients with exacerbation of known systolic heart failure and fluid overload despite standard therapy.[14] Within 72 hours, patients were randomized to standard therapy plus placebo or standard therapy plus one of three doses (30, 60, or 90 mg/day) of tolvaptan. Treatment was intended to continue in the outpatient setting, for up to 60 days total, but 77 of the patients discontinued outpatient study participation. The most robust data, therefore, come from the in-hospital course of therapy.

In hospitalized patients, each 3-mEq decrease in serum sodium is associated with a 20% increase in 60-day mortality

The primary endpoint was body weight change at 24 hours. The median body weight at 24 hours decreased by approximately 2 kg in the tolvaptan groups compared with 0.60 kg in the placebo group ($P \leq .008$ for all tolvaptan groups vs placebo). The change in body weight with tolvaptan was not dose-dependent and was sustained throughout the hospitalization (Figure 4).[14]

Decrease in signs of congestion

At the time of discharge, fewer patients treated with tolvaptan had dyspnea, jugular venous distention, and edema compared with placebo recipients, but only the difference in dyspnea reached statistical significance (P = .04).[14]

Favorable safety profile

As in the outpatient study discussed above,[12] there were no changes in blood pressure,

AVP antagonism rapidly raises serum sodium in hyponatremic patients

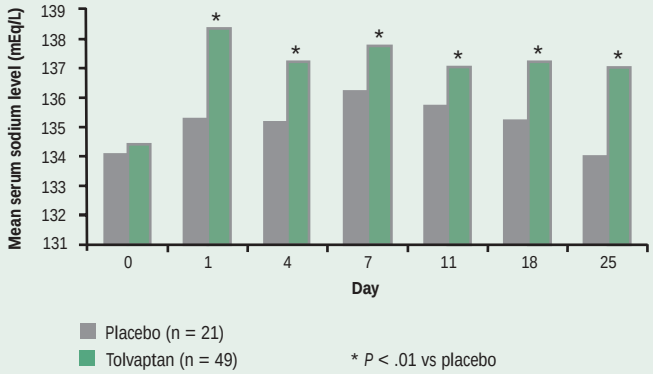

FIGURE 3. In chronic heart failure patients with hyponatremia (mean serum sodium levels < 136 mEq/L), tolvaptan improved serum sodium levels starting on day 1, an improvement that was sustained over the 25-day duration of the study. Tolvaptan results are pooled from the study's three dose groups (30, 45, and 60 mg/day). Data from reference 12.

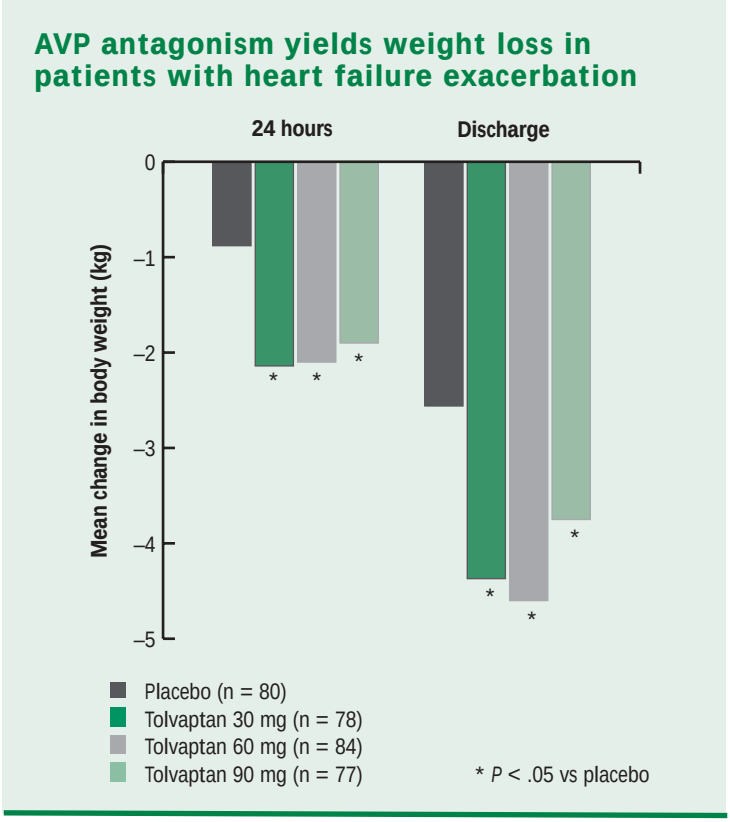

FIGURE 4. In patients hospitalized with a heart failure exacerbation, tolvaptan administration at any dose was associated with weight loss at 24 hours after administration, with further weight loss until discharge. Data from reference 14.

heart rate, serum creatinine levels, or blood urea nitrogen (BUN) levels in tolvaptan recipients in this inpatient trial, and serum potassium levels also remained unchanged despite the loss in body weight.[14]

Normalization of serum sodium is sustained

Also in accordance with the outpatient studies, serum sodium levels normalized within 1 day of initiating tolvaptan in the 30% of patients with hyponatremia (mean serum sodium ≤ 135 mEq/L) at randomization, and this normalization was sustained throughout the study.[14]

Decrease in mortality with elevated BUN, severe congestion

There were no differences between groups in in-hospital mortality or the incidence of worsening heart failure, defined as death, rehospitalization, or unscheduled visits for heart failure.[14]

A post hoc analysis uncovered a reduction in 60-day mortality in the combined tolvaptan groups compared with the placebo group among patients with elevated BUN levels (> 29 mg/dL) and among those with severe systemic congestion at randomization (defined as the presence of edema, dyspnea, and jugular venous distention). Although these differences reached statistical significance ($P < .05$), this post hoc analysis is useful only for generating hypotheses and requires confirmation in larger studies. Of note, all-cause mortality at 60 days was more than triple in patients with mild hyponatremia compared with normal serum sodium levels, was increased fivefold in patients with elevated vs normal levels of BUN, and was more than double in patients with severe congestion compared with patients without severe congestion.[14]

SUMMARY AND FUTURE RESEARCH

AVP receptor antagonists have many favorable properties compared with loop diuretics. Loop diuretics decrease serum sodium levels, serum potassium levels, plasma osmolality, renal blood flow, and GFR; may precipitate orthostatic hypotension; activate neurohormones such as norepinephrine and plasma renin; and may increase BUN/serum creatinine levels. In contrast, the V_2 receptor antagonist tolvaptan normalizes or improves serum sodium levels; has no effect on serum potassium levels, blood pressure, BUN/creatinine levels, and neurohormonal activity; increases plasma osmolality; and may increase renal blood flow and GFR. The increase in plasma osmolality may explain the enhanced diuresis with tolvaptan compared with loop diuretics.

The AVP receptor antagonist tolvaptan is the best-studied AVP receptor antagonist in heart failure to date. When added to standard therapy, it produces rapid and sustained decreases in body weight in hospitalized and ambulatory patients with congestive heart failure. Tolvaptan use is associated with normalization of serum sodium in patients with mild hyponatremia. The addition of tolvaptan did not cause acute or chronic changes in blood pressure, heart rate, serum potassium, BUN, or creatinine. There is no apparent dose effect among the three doses of tolvaptan tested (30, 60, and 90 mg/day).

Whether these encouraging changes in surrogate markers with AVP antagonist therapy will translate to improved clinical outcomes is being investigated in a multicenter, double-blind, placebo-controlled clinical trial involving more than 4,000 patients hospitalized with worsening congestive heart failure. Patients have been randomized to tolvaptan 30 mg/day or standard care for a minimum of 60 days, with the primary endpoints being time to all-cause mortality and time to cardiovascular mortality or hospitalization for heart failure.[15] Preliminary results are expected at the end of 2006.

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