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REVIEW

Managing Hyponatremia in Patients With Heart Failure

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Approximately 20% of heart failure patients have low levels of serum sodium, often at a time when they are hospitalized during a period of decompensation. The presence of hyponatremia adversely affects outcomes in heart failure and is associated with impaired cognitive and neuromuscular function. Current strategies for treating hyponatremia in heart failure patients have limited efficacy. Although the development of hyponatremia in heart failure patients is polyfactorial, the nonosmotic release of arginine vasopressin (AVP) from the posterior pituitary plays a dominant role in this process through its effects on regulating the absorption of free water in the distal portion of the nephron. Drugs which block the effects of AVP on the V2 receptor have been shown to increase serum sodium by promoting the excretion of free water from the kidney. In this review, the theoretical basis supporting the use of AVP blockers is discussed and results from clinical trials in which they were administered to euvolemic and hypervolemic patients are reviewed. Administration of AVP blockers to heart failure patients increases free water excretion, promotes weight loss, and increases serum sodium levels without significant major adverse effects. Clinical trial results demonstrate safety during long-term administration. These findings indicate that the use of AVP receptor antagonists should be considered in heart failure patients who have evidence of significant hyponatremia. ***Journal of Hospital Medicine*** **2010;5:S33–S39.** © *2010 Society of Hospital Medicine.*

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Heart failure is a common and growing problem in both industrialized and developing nations. In the U.S. alone there are estimated to be well over 5 million heart failure patients and that number is expected to double over the next few decades. There are several reasons for this pandemic, most notably the aging of the world's population, a rising incidence of heart failure risk factors including hypertension, diabetes and obesity, and improved survival post-myocardial infarction (MI).[1] Greater longevity of patients with existing heart failure as a result of treatment with drugs and devices that lower mortality and, in developing nations, a reduction in premature mortality from infectious diseases have also contributed to the increase in heart failure prevalence. Although there have been important advances in treating heart failure that have improved outcomes over the past several decades, morbidity and mortality remain unacceptably high and quality of life is substantially reduced. Thus, there is considerable need for finding new approaches for managing patients with this condition.

The Role of Neurohormonal Blockade in the Treatment of Heart Failure Patients

The pathophysiology of heart failure is complex. In patients who develop systolic dysfunction, the pathway initially involves injury to the heart and/or increases in wall stress which activates a variety of compensatory responses in an effort to reestablish homeostasis within the cardiovascular (CV) system. Many of these responses are mediated by neurohormonal systems that are stimulated both systemically and locally within the heart itself.[2,3] While this widespread neurohormonal activation has some short-term benefits in maintaining cardiac performance, there is clear evidence that it has adverse effects when maintained over time. The deleterious effects of neurohormonal activation in heart failure include excess salt and water retention, constriction of arterial resistance and venous capacitance vessels, increased load on the heart, electrolyte abnormalities and maladaptive cardiac remodeling. The critical role of neurohormonal activation in the pathogenesis and progression of heart failure has been confirmed by the results of large scale clinical trials which show that neurohormonal blocking agents such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs), and aldosterone blockers greatly reduce morbidity and mortality and result in a variety of other favorable effects in heart failure patients.[4–9] Based on their profound effects on outcomes, strategies that target neurohormonal activation have emerged over the past 2 decades as the cornerstone of medical management of heart failure.

Establishing Risk in Heart Failure

Although there have been impressive gains in reducing morbidity and mortality in heart failure patients over the past 3 decades, the overall clinical course remains unfavorable in a substantial portion of this population. A wide variety of risk factors which identify patients who are more likely to do poorly in the future have been identified. These include demographic variables (eg, age), functional and structural

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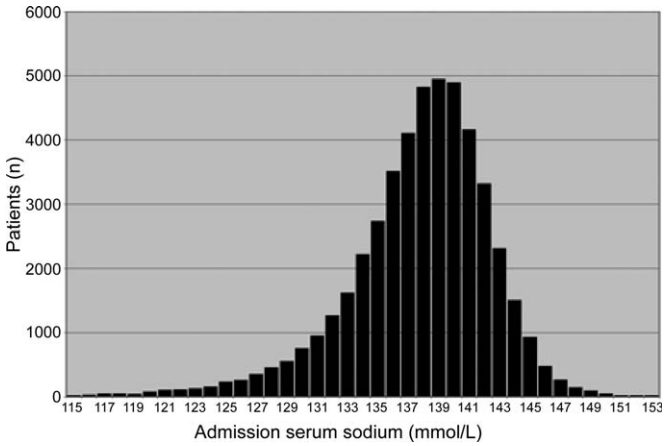

FIGURE 1. Distribution of admission serum sodium in patients hospitalized with a primary discharge diagnosis of heart failure.

abnormalities, hemodynamic measurements, symptomatic status, exercise capacity, quality of life, presence of comorbidities and a myriad of blood tests and biomarkers. Amongst the plethora of risk factors for poor outcome, decompensation of heart failure which results in hospitalization has been recognized as 1 of the most important prognostic indicators. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) Registry which included a large fairly representative population of heart failure patients from throughout the U.S. followed a subset of patients for 60 days to 90 days immediately post-discharge from a hospitalization that was associated with decompensated heart failure.[10] Over this relatively short time period hospital readmission rate was over 30% and mortality over 9%. Thus, within 2 months to 3 months of discharge following an episode of decompensation ~40% of heart failure patients had either died or were back in the hospital. Among the many risk factors that have been used to predict morbidity and mortality outcomes either during or following hospitalization, the ones that appear to be the most powerful in detecting patients who are likely to do poorly are impaired renal function,[11,12] low systolic blood pressure,[13] persistence of congestion at the time of hospital discharge,[14] elevation of various biomarkers such as B-type natriuretic peptide (BNP)[15] and the presence of hyponatremia.[16]

Hyponatremia in Heart Failure

Incidence of Hyponatremia in Heart Failure Patients

Determining the exact incidence of hyponatremia in heart failure patients has been challenging due to differences in the populations that have been studied and in the criteria used to define hyponatremia. The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) study reported that 21.3% of the cohort of hospitalized patients had a serum sodium below 136 mmol/L.[17] Higher incidences were reported in the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) which found that 27% of patients had serum sodium concentrations between 132 mmol/L to 135 mmol/L.[18] The Evaluation Study of CHF and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial reported that 18% of patients had hyponatremia defined as serum sodium concentration below 134 mmol/L.[19] Data from OPTIMIZE-HF, a registry that captured data from a large cohort of representative patients who were hospitalized with decompensated heart failure indicate that such patients have a wide distribution of admission sodium values (Figure 1).[16] Overall, 19.7% of the OPTIIMIZE-HF patients had values below 135 mmol/L.

Risk Associated With Hyponatremia

There is considerable evidence that hyponatremia is associated with increased risk for poor outcomes in heart failure patients. One of the first reports that related hyponatremia to a poor prognosis came from Lee and Packer who analyzed 30 clinical, hemodynamic, and biochemical variables in outpatients with severe heart failure.[20] Their results showed that serum sodium was the most powerful predictor of CV mortality. Similar findings have been reported by other investigators.[21] In patients hospitalized for decompensated heart failure, the presence of hyponatremia has been shown to be an independent predictor of longer duration of stay.[22] Results from the OPTIMIZE-HF Registry confirmed the adverse impact of hyponatremia on length of stay during a heart failure hospitalization and also suggested that low serum sodium was associated with significantly higher in-hospital and post-discharge mortality rates.[16] In this large cohort of hospitalized patients with decompensated heart failure, each 3 mmol/L decrease in serum sodium below 140 mmol/L increased the risk of in-hospital and follow-up mortality by 19.5% and 10%, respectively. This association is depicted in Figure 2. A similar adverse impact of hyponatremia on post-discharge outcomes was seen in the results of the ACTIV in CHF study.[17] Overall, 69 patients out of a total of 319 who were included in the study (21.6%) had a serum sodium that was $<$136 mmol/L. Mortality over a 60 day period of follow-up was 14.5% in the hyponatremic patients compared to 4% in the 250 patients whose serum sodium was $\geq$136 mmol/L.

Although these data present a powerful argument that hyponatremia is a potent risk factor for poor outcomes in heart failure patients both during and following hospitalization, they do not determine whether or not the relationship is causal. It is possible that the poor outcomes that have been observed in hyponatremic patients are related to an association between low serum sodium levels and the more profound alterations in hemodynamics, neurohormonal activation and renal function that are seen in patients with advanced heart failure. Alternatively, increased edema in vital organs including the heart in hyponatremic patients could further impair already tenuous function and

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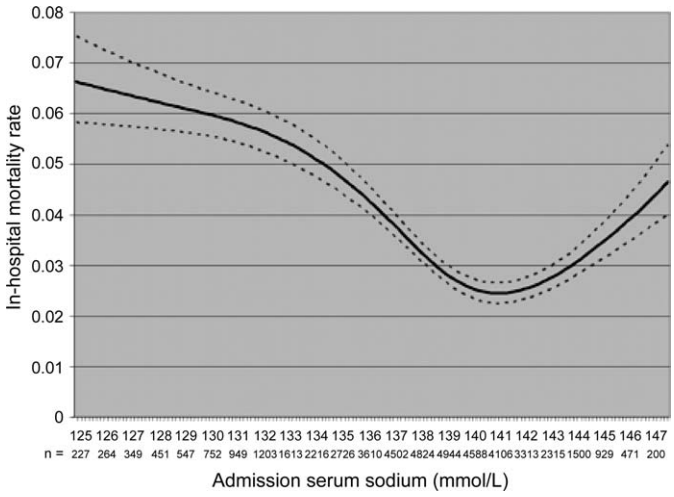

FIGURE 2. Relationship between admission serum sodium level and in-hospital mortality. Restrictive cubic spline transformation plot with 95% confidence intervals is shown.

contribute to a downward spiral in the clinical course. The impact of hyponatremia in limiting the use of loop diuretics and spironolactone may also be associated with a less favorable long-term outcome. The presence of hyponatremia may also contribute to a poor outcome as a result of effects on cognitive and neuromuscular function.[23,24] Impaired cognition could adversely affect compliance with the medical regimen while neuromuscular problems related to hyponatremia could contribute to an increased incidence of falls and other traumatic injuries that older patients with chronic diseases are already at high risk of experiencing.

Pathophysiology of Hyponatremia

The pathophysiology of hyponatremia in heart failure patients involves several different processes.[25] Overall, heart failure is characterized by retention of excessive amounts of salt and water in the body. Sodium retention is related to decreased renal perfusion that is caused by the effects of reduced cardiac output, decreased renal perfusion pressure and increased afferent glomerular arteriolar resistance. A reduction in glomerular filtration and increased reabsorption of sodium and water in the proximal renal tubules leads to a reduction in the delivery of water and solute to the diluting segment of the nephron. In patients with heart failure the renin-angiotensin system (RAS) is activated, an event that is further stimulated by the administration of loop diuretics.[26] Angiotensin II (Ang II), a key effector molecule of the RAS, increases tone in renal efferent arterioles. This tends to enhance both sodium and water reabsorption both through an increase in the glomerular filtration fraction and by direct effects on the distal tubule.[27] Ang II also stimulates the thirst center of the brain both directly and through stimulation of antidiuretic hormone to promote the ingestion of excessive amounts of hypotonic fluids.[25] Water reabsorption in the distal portion of the nephron is governed by arginine vasopressin (AVP). High levels of AVP are seen in patients with heart failure[26,28] and there is a significant association between serum levels of this peptide and the symptomatic state of the patient. There is evidence that in heart failure patients AVP levels are elevated disproportionally to plasma osmolality and serum sodium concentrations.[28,29] Even when serum osmolality is increased in this setting by infusion of sodium, AVP levels fail to demonstrate an appropriate reduction suggesting that mechanisms other than activation of osmoreceptors are involved. The effects of AVP in the pathogenesis of hyponatremia are significant. This peptide binds to the vasopressin-2 (V2) receptor in the collecting duct of the kidney stimulating an increase in the second messenger cyclic AMP.[30] Downstream signaling initiated by cyclic AMP leads to an increase in the number and activation of aquaporin-2 water channels on the luminal surface of epithelial cells in the collecting tubule.[31] The presence of these activated pores is necessary for water permeability in the collecting duct and leads to an increase in the reabsorption of free water. Finally, the use of diuretics in the treatment of heart failure has been implicated in the development and worsening of the hyponatremic state.[32]

Treatment of Hyponatremia

Treatment options for dealing with hyponatremia in heart failure patients have been limited until recently. Since low cardiac output and/or diminished renal perfusion are involved, interventions which improve cardiac and renal function can reverse hyponatremia. While this can be accomplished by the use of inotropic agents, the use of drugs such as dobutamine, milrinone, and other inotropes in either stable or decompensated heart failure patients with adequate tissue perfusion is not routinely recommended due to a well-documented increase in adverse effects, particularly in patients with coronary artery disease.[33] The use of hypertonic saline is also not recommended since it may worsen the extent of volume overload in decompensated patients. Fluid restriction can be used to treat hyponatremia, particularly in hospitalized patients where stricter control on input is possible. Hyponatremic patients, however, often experience excessive thirst and restriction to less than 1000 cc to 1500 cc is rarely, if ever, successful for more than a brief period of time. The use of angiotensin converting enzyme (ACE) inhibitors has been associated with an improvement in serum sodium levels. Packer et al. treated a cohort of heart failure patients who were receiving a stable dose of diuretic with an ACE inhibitor captopril and found that over a 2-week period the serum sodium increased from 131.2 $\pm$ 0.5 to 135.9 $\pm$ 0.5 mmol/L; $P < 0.001$).[34] These investigators concluded that the RAS was involved in the pathogenesis of hyponatremia and that ACEIs increased sodium levels in hyponatremic patients, though the mechanism through which this occurs has not been delineated.

The Use of Vaptans in Treating Hyponatremia

AVP actions are mediated by an interaction of the peptide with a series of receptors located on cells throughout the

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body. Vaptans are nonpeptidergic agents which block the interaction of AVP with these receptors; they are classified according to which receptor subtype they affect. As mentioned earlier, activation of the V2 receptor on renal tubular cells increases collecting duct permeability to water and leads to reabsorption of free water.[35] The V1A receptor is located on vascular smooth muscle cells where it mediates an increase in vasomotor tone. V1A receptors are also found on platelets and in the myometrium where they mediate aggregation and uterine contraction, respectively. Some of the AVP antagonists (eg, conivaptan) block both the V1A and V2 receptors while others (eg, tolvaptan and lixivaptan) are selective for the V2 receptor.

Tolvaptan, a V2 selective agent, has been studied extensively in heart failure as well as in patients with hyponatremia due to a variety of causes. One of the initial studies was performed in a group of 254 heart failure patients who were randomized to receive tolvaptan in doses ranging from 30 mg to 60 mg daily or placebo.[36] Tolvaptan at all doses studied was associated with significant reductions in body weight and improvement in the signs and symptoms of heart failure. All doses were also associated with an increase in serum sodium levels in this study. Patients who were hyponatremic made up 28% of the study population and these patients experienced the greatest increase in serum sodium. Of note was the fact that as early as day 1 in the study 80% of tolvaptan (as opposed to 40% of placebo) patients had normalization of their serum sodium levels. These effects occurred without significant changes in blood pressure or renal function and the major side effects that were seen were polyuria, dry mouth, and thirst. This study was followed by the ACTIV in CHF trial which included a slightly larger population of 319 patients (of whom 21.3% were hyponatremic at baseline) who were hospitalized due to decompensated heart failure.[17] Mean body weight decreased significantly more in patients treated with tolvaptan compared to those who received placebo. Tolvaptan-treated patients also experienced increases in serum sodium that were greatest in the patients who were hyponatremic at baseline. These changes persisted throughout the duration of the study. On post hoc analysis, event-free survival tended to be longer for the combined group of patients treated with tolvaptan compared to placebo but there were no differences in the rate of rehospitalization or unscheduled visits for heart failure. As in the initial study, tolvaptan was well tolerated, with dry mouth being the main side effect. There were no significant hemodynamic or renal effects.

The efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) study randomized 4133 patients hospitalized for decompensated heart failure to receive either tolvaptan 30 mg daily or placebo in addition to their standard therapy. The short-term goal of the study was to assess the effects of therapy on a composite end-point of patient assessed global clinical features and weight loss on day 7 (or at the time of hospital discharge) after starting treatment.[37] The results of EVEREST demonstrated that patients treated with tolvaptan had greater improvement in the composite primary end-point. This effect was driven by a greater reduction in body weight with active drug. Although, changes in global clinical status did not differ between the study groups, tolvaptan-treated patients reported significantly greater improvement in dyspnea at day 1. In 1 (but not the other of the 2 component trials of EVEREST) there was also an improvement in edema. At day 1 and at discharge, the tolvaptan group with hyponatremia (defined as a serum sodium below 134 mEq/L) demonstrated significantly greater increases in serum sodium than in the hyponatremic placebo treated patients. Tolvaptan was well tolerated and serious adverse event frequencies were similar between groups, without excess renal failure or hypotension.

Patients who were enrolled in EVEREST were then followed for an average of 9.9 months on tolvaptan or placebo in order to assess the effects of treatment on the dual primary endpoints of all-cause mortality (both superiority and noninferiority) and CV death or heart failure hospitalization.[38] The results demonstrated no significant differences in either primary or secondary morbidity and mortality outcomes between tolvaptan and placebo treated patients. In the EVEREST patients with baseline serum sodium levels less than 134 mEq/L, there was a significant increase of 5.49 mEq/L $\pm$ 5.77 mEq/L (mean $\pm$ SD) at day 7 or discharge, if earlier, with tolvaptan, compared with 1.85 mEq/L $\pm$ 5.10 mEq/L in the placebo group. This effect was observed as early as day 1 and was maintained throughout the 40 weeks of treatment. Side effects were minimal. Overall, tolvaptan increased thirst and dry mouth, but the frequencies of major adverse events were similar in the 2 groups.

Two parallel multicenter, randomized, double-blind, placebo-controlled trials, termed collectively the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT-1 and SALT-2), examined the effect of tolvaptan on hypervolemic and euvolemic hyponatremia of diverse causes.[39] The 448 patients included in the 2 studies were randomly assigned to either placebo or tolvaptan starting at a dose of 15 mg daily (increasing to 30 mg and then 60 mg if needed, depending on serum sodium concentrations) and followed over a 30 day period. The population included 138 patients (31%) with chronic heart failure as the cause of hyponatremia with the remainder of the population divided between patients with cirrhosis or syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) and other causes of hyponatremia. The 2 primary end points for all patients were the change in the average daily area under the curve for the serum sodium concentration from baseline to day 4 and the change from baseline to day 30. As shown in Figure 3, serum sodium concentrations increased significantly more in the tolvaptan group than in the placebo group during the first 4 days and after the full 30 days of therapy. A planned analysis of the SALT trials demonstrated that correction of hyponatremia with tolvaptan was

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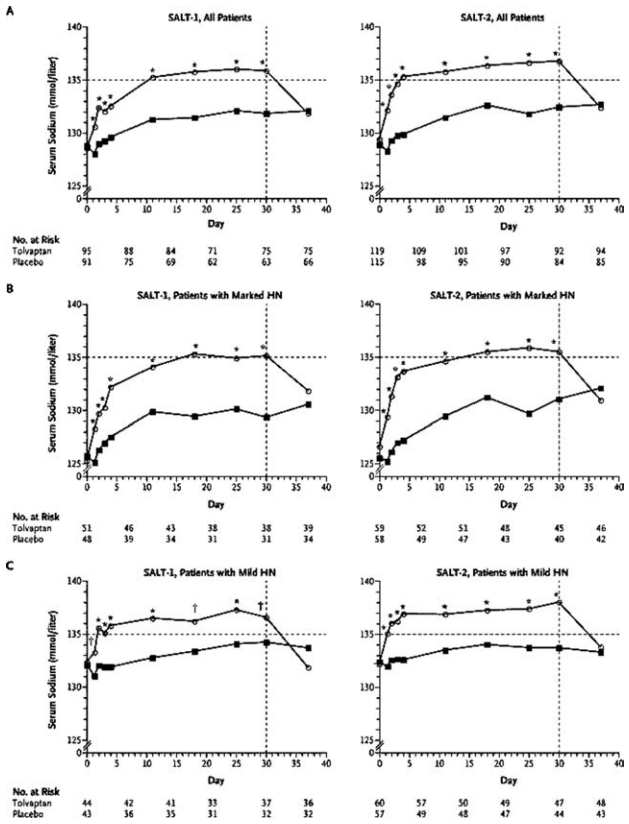

FIGURE 3. Mean serum sodium concentrations according to the day of patient visit in the SALT-1 and SALT-2 trials. Schrier RW, Gheorghiade M, Berl T, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099–2112. Copyright 2006 Massachusetts Medical Society. All rights reserved. Asterisks indicate $P < 0.001$ for the comparison between tolvaptan and placebo treated patients. Daggers indicate $P < 0.01$ for the comparison between tolvaptan and placebo. Tolvaptan was discontinued on day 30. Circles denote patients receiving tolvaptan, and squares denote patients receiving placebo. Horizontal lines indicate the lower limit of the normal range for the serum sodium concentration. Vertical lines indicate the end of the treatment period. HN denotes hyponatremia. Abbreviation: SALT-1/SALT-2, Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2.

associated with significant improvement in self-reported mental status, particularly in patients with marked hyponatremia or SIADH. Improvements in mental health scores were positively correlated with changes in serum [Na+] in both the tolvaptan and placebo groups and reversed after cessation of therapy, suggeting that hyponatremia-associated impairments in mental function can be significantly improved by raising the serum [Na+]. The major side effects with tolvaptan included increased thirst, dry mouth, and increased urination. Tolvaptan has been approved by the US Food and Drug Administration (FDA) for the treatment of euvolemic and hypervolemic hyponatremia.

Lixivaptan is another selective V2 receptor antagonist that has been studied in heart failure patients.[40] In a randomized, double-blind, placebo-controlled, ascending single-dose study 42 diuretic-requiring patients with mild-to-moderate heart failure patients received either placebo or doses of lixivaptan ranging from 10 mg to 400 mg. Except for patients who received the 10-mg dose, lixivaptan produced a significant and dose-related increase in urine volume over a 4-hour period compared with placebo. Over 24 hours increases in urine volume were greater with lixivaptan than with placebo and these increases were accompanied by significant increases in solute-free water excretion. At higher doses of lixivaptan, serum sodium levels increased significantly. The drug was tolerated in these patients and side effects tended to be mild. The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE Study) is an on-going trial that is designed to evaluate whether lixivaptan is an effective and safe agent for increasing serum sodium in heart failure patients who are volume overloaded and have hyponatremia. The secondary end-points of the BALANCE study include all-cause mortality, CV effects, HF hospitalization and acute change in body weight.

The combined V1A and V2 receptor antagonist conivaptan has been approved by the FDA for the treatment of euvolemic and hypervolemic hyponatremia. The acute hemodynamic effects were studied in 142 NYHA class III and IV heart failure patients. Administration of 20 mg or 40 mg of conivaptan significantly reduced pulmonary artery wedge and right atrial pressures during the 3-hour to 6-hour interval after intravenous administration and significantly increased urine output in a dose-dependent manner during the first 4 hours after the dose.[41] In another study 170 patients hospitalized for worsening heart failure were randomly assigned to treatment with conivaptan (20-mg loading dose followed by 2 successive 24-hour continuous infusions of 40, 80, or 120 mg/day) or placebo in addition to their standard therapy.[42] At 24 hours each dose of conivaptan had increased urine output significantly more than placebo with the difference averaging 1.0 to 1.5 L. The mean increase in serum sodium at 24, 48, and 72 hours was significantly higher in each of the conivaptan groups compared with the placebo group. At 48 hours, conivaptan increased serum sodium by 2.25 mmol/L to 3.27 mmol/L more than placebo. Conivaptan was well tolerated in these hospitalized heart failure patients. Infusion-site reactions for this drug which is given intravenously were the most common adverse event and administration of the drug was not associated with clinically important changes in vital signs, electrolyte disturbances, or cardiac rhythm.

The effects of conivaptan on serum sodium levels were evaluated in 84 hospitalized patients with euvolemic or hypervolemic hyponatremia defined as a serum sodium between 115 mEq/ to 129 mEq/L.[43] These patients received either intravenous placebo or conivaptan administered as a 30-minute, 20-mg loading dose followed by a 96-hour infusion of either 40 mg/day or 80 mg/day. The results which are depicted in Figure 4 show that both conivaptan doses

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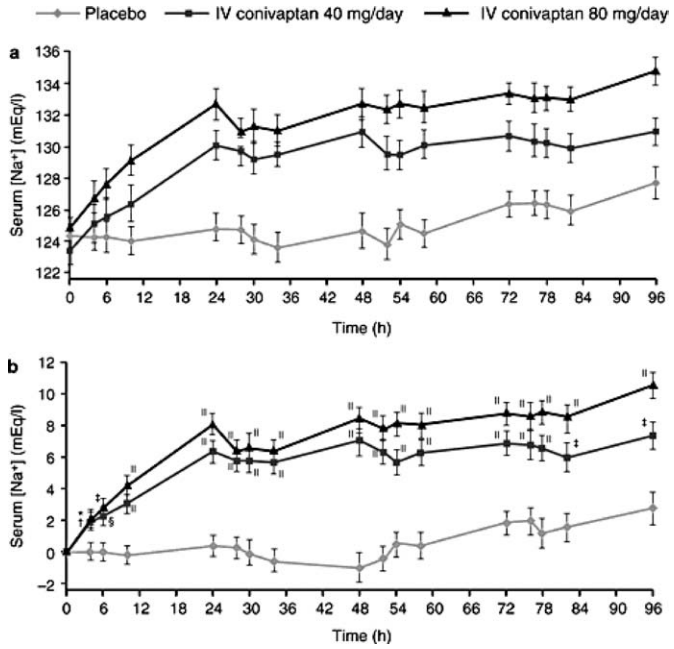

FIGURE 4. (a) Mean serum [Na^+] and (b) mean change (LS) from baseline in serum [Na^+] at baseline (hour 0) and each measurement time. T bars indicate SE. $^*P = 0.025$; $\dagger P = 0.034$; $\ddagger P = 0.002$; $\S P = 0.008$; $\| P < 0.001$.

were associated with highly significant increases under the sodium-time curve during the 4-day treatment. From baseline to the end of treatment, serum sodium increased by 0.8 ± 0.8 mEq/L with placebo as compared to 6.3 ± 0.7 mEq/L and 9.4 ± 0.8 mEq/L with the 40 mg and 80 mg doses of conivaptan. Conivaptan was generally well tolerated, although infusion-site reactions led to the withdrawal of 1 (3%) and 4 (15%) of patients given conivaptan 40 mg/day and 80 mg/day, respectively.

The overall safety profile of the vaptans has been good. Most of the adverse effects including thirst, dry mouth and others have been minor and these agents, in general, have only minimal effects on blood pressure and renal function. In addition, the long-term safety and tolerability of tolvaptan was demonstrated in the EVEREST trial. One theoretical concern about the use of vaptans to treat hyponatremia is that rapid correction of hyponatremia at a rate of >12 mEq/L over 24 hours can cause osmotic demyelination of brain structures with severe neurologic consequences. It has been advised that in susceptible patients (including those with severe malnutrition, alcoholism, or advanced liver disease) that sodium levels be corrected at a lower rate. It is also recommended that the drugs be initiated in hospital and that serum sodium is monitored during treatment.

Conclusions

Hyponatremia is common in heart failure patients, particularly during periods of decompensation. The presence of hyponatremia has been associated with a substantial increase in risk for longer hospitalization stay and mortality both in the hospital and following discharge. Hyponatremia has also been associated with alterations in cognitive and neuromuscular function which could further impair heart failure patients, particularly those who are elderly. The use of AVP receptor antagonists to treat hyponatremia is based on evidence that this peptide which regulates the flow of free water in the distal portion of the nephron is inappropriately elevated in heart failure patients. Administration of AVP receptor antagonists has been shown to increase and improve free water excretion and increase serum sodium levels in both euvolemic and volume overloaded hyponatremic patients. In addition to their favorable effects on serum sodium levels, the AVP receptor blockers have been shown to improve hemodynamics acutely and to increase weight loss in heart failure patients. There is some evidence that they also improve symptoms in hospitalized patients and that correction of hyponatremia is associated with improved cognitive and neuromuscular function. Currently available evidence, however, does not support a beneficial effect on long-term outcomes such as mortality or CV hospitalizations. Additional on-going clinical trials will provide further insights into this critical question. The overall side effect profile of the vaptans is favorable and published studies document the long-term safety of administration of tolvaptan in heart failure patients. Thus, these agents represent an important new approach for treating hyponatremia in heart failure patients. They deserve consideration for use when hyponatremia is present during an episode of decompensated heart failure.

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References

1. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2008;117:2544–2565.
2. Rouleau JL, Moye LA, de Champlain J, et al. Activation of neurohumoral systems following acute myocardial infarction. *Am J Cardiol.* 1991;68: 80D–86D.
3. Dostal DE, Baker KM. The cardiac renin-angiotensin system: conceptual, or a regulator of cardiac function? *Circ Res.* 1999;85:643–650.
4. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med.* 1991;325:293–302.
5. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet.* 2003;362:772–776.
6. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after

2010 Society of Hospital Medicine DOI 10.1002/jhm.792
Published online in Wiley OnlineLibrary (wileyonlinelibrary.com).

myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators [see comments]. *N Engl J Med.* 1992;327: 669–677.
7. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334:1349–1355.
8. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341:709–717.
9. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309–1321.
10. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med.* 2008;168:847–854.
11. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA.* 2005;293: 572–580.
12. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 2004;43:61–67.
13. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA.* 2006;296:2217–2226.
14. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J.* 2000;140:840–847.
15. Maisel A, Mueller C, Adams K Jr, et al. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail.* 2008;10: 824–839.
16. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J.* 2007;28:980–988.
17. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA.* 2004;291:1963–1971.
18. Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation.* 2005;111:2454–2460.
19. Gheorghiade M, Rossi JS, Cotts W, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med.* 2007;167:1998–2005.
20. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation.* 1986;73:257–267.
21. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol.* 2002;40:1801–1808.
22. Krumholz HM, Chen YT, Bradford WD, Cerese J. Variations in and correlates of length of stay in academic hospitals among patients with heart failure resulting from systolic dysfunction. *Am J Manag Care.* 1999;5: 715–723.
23. Pereira AF, Simoes do CF, de MA. The use of laboratory tests in patients with mild cognitive impairment. *J Alzheimers Dis.* 2006;10:53–58.
24. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.* 2006;119:71–78.
25. Sica DA. Hyponatremia and heart failure--pathophysiology and implications. *Congest Heart Fail.* 2005;11:274–277.
26. Francis GS, Benedict C, Johnstone DE et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation.* 1990;82:1724–1729.
27. Schuster VL, Kokko JP, Jacobson HR. Angiotensin II directly stimulates sodium transport in rabbit proximal convoluted tubules. *J Clin Invest.* 1984;73:507–515.
28. Goldsmith SR, Francis GS, Cowley AW Jr. Arginine vasopressin and the renal response to water loading in congestive heart failure. *Am J Cardiol.* 1986;58:295–299.
29. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. *Am J Physiol.* 1979;236:F321–F332.
30. Verbalis JG. Vasopressin V2 receptor antagonists. *J Mol Endocrinol.* 2002; 29:1–9.
31. Nielsen S, Kwon TH, Christensen BM, Promeneur D, Frokiaer J, Marples D. Physiology and pathophysiology of renal aquaporins. *J Am Soc Nephrol.* 1999;10:647–663.
32. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest.* 1993;103:601–606.
33. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol.* 2003;41:997–1003.
34. Packer M, Medina N, Yushak M. Correction of dilutional hyponatremia in severe chronic heart failure by converting-enzyme inhibition. *Ann Intern Med.* 1984;100:782–789.
35. Birnbaumer M. Vasopressin receptors. *Trends Endocrinol Metab.* 2000;11: 406–410.
36. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation.* 2003;107:2690–2696.
37. Gheorghiade M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA.* 2007;297: 1332–1343.
38. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007;297:1319–1331.
39. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006; 355:2099–2112.
40. Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW. Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol.* 2006;47:1615–1621.
41. 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.
42. 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;14:641–647.
43. Zeltser D, Rosansky S, van RH, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol.* 2007;27:447–457.

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