Hyponatremia in Patients with Heart Failure

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Mild hyponatremia is encountered frequently in patients hospitalized for worsening heart failure. Admission plasma sodium concentration appears to be an independent predictor of increased mortality after discharge and rehospitalization. Recent studies have suggested that correction of hyponatremia may be associated with improved survival. This hypothesis is currently being studied in large prospective randomized clinical trials. **(Am J Cardiol 2005; 96[suppl]:19L–23L)**

Hyponatremia, defined as a decrease in plasma sodium concentration to a level <136 mEq/L [1 mEq/L = 1 mmol/L], is an electrolyte abnormality frequently encountered in hospitalized patients.[1,2] Hyponatremia may be seriously underreported because patients are often hospitalized for other reasons and develop electrolyte abnormalities during hospitalization.[3–5] The actual incidence of hyponatremia in hospitalized patients depends on the nature of the patient population as well as on the specific plasma sodium values used to establish the diagnosis. Previous reports have estimated the incidence to be 20% among hospitalized patients if hyponatremia is defined as a plasma sodium level <136 mEq/L, and 1% to 4% if it is defined as plasma sodium level ≤130 mEq/L.[6–11]

Severe hyponatremia is a potentially serious clinical condition that may lead to severe neurologic manifestations. Symptoms generally occur at plasma sodium concentrations <125 mEq/L. The mortality rates associated with hyponatremia range from 5% to 50% depending on severity and acuity of onset.[12]

Prognostic Significance of Mild Hyponatremia in Patients Hospitalized for Heart Failure

In the last few years, several studies demonstrated that admission plasma sodium concentration is an independent predictor of increased rates of rehospitalization and mortality in patients hospitalized for heart failure (HF).

In a randomized trial assessing the effect of a nurse-directed multidisciplinary intervention on readmissions in 282 patients hospitalized for worsening HF, decreasing plasma sodium level was an independent predictor of readmission.[13] A 3-mEq/L decrease in the admission level of plasma sodium concentration was associated with a 20% relative increase in readmissions within 90 days of discharge.

In a retrospective review of 4,031 medical records of hospitalized patients with HF, hyponatremia was associated with a significant 50% increase in 30-day all-cause mortality; this mortality increase was also maintained at 1 year when compared with patients with normal plasma sodium concentrations.[14]

These findings were also reported in retrospective analyses of large randomized clinical trials. In a risk-stratification model using data from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), low plasma sodium level on admission was identified as 1 of the 5 predictors of 60-day mortality.[15,16] Considering data from the same trial, Klein and associates[17] investigated the relation between admission plasma sodium concentration and the number of days hospitalized for cardiovascular causes within 60 days of discharge, in-hospital mortality, 60-day mortality, and 60-day mortality/rehospitalization.[17] In this analysis, the number of days hospitalized for cardiovascular causes was 33% higher in the lowest plasma sodium quartile than in the other quartiles. Patients in the lowest plasma sodium quartile also had a 2-fold higher in-hospital and 60-day mortality than patients in the other plasma sodium quartiles.[17] A 3-mEq/L decrease in plasma sodium concentration from the admission level was associated with an 18% relative increase in mortality within 60 days of discharge.[17]

The association of hyponatremia on admission with the 60-day postdischarge mortality in hospitalized patients with HF was seen in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV-CHF) trial.[18] In a retrospective analysis of this study, patients with hyponatremia had a 3-fold increase in 60-day mortality compared with normonatremic patients.[19]

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The correlation of hyponatremia with hemodynamics in patients hospitalized for HF has been studied in a post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE).[20] In this trial, 433 patients with severe HF and reduced ejection fraction were randomized to management guided by pulmonary artery catheters or by clinical assessment alone. In this study, 18% of the patients had persistent hyponatremia (plasma sodium level <134 mEq/L throughout hospitalization). These patients had a higher pulmonary capillary wedge pressure and right atrial pressure after treatment than patients with normal plasma sodium levels, despite receiving higher diuretic doses and undergoing similar reductions in body weight.[20] In addition, plasma sodium concentration on discharge was a significant predictor of subsequent mortality and of rehospitalization for HF.[20]

Role of Hyponatremia in the Pathophysiology of Heart Failure

In patients with worsening HF, decreased stimulation of mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles leads to increased sympathetic discharge, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin among other neurohormones.[21] Despite increased total fluid volume, increased sympathetic drive contributes to avid sodium and water retention,[21,22] and the enhanced vasopressin release results in an increased number of aquaporin water channels in the collecting duct of the kidney that promote abnormal free water retention and contribute to the development of hypervolemic hyponatremia.[23,24]

Higher circulating levels of catecholamines, renin, angiotensin II, aldosterone, and vasopressin have been observed in patients with HF and hyponatremia than in normonatremic patients.[25–27] Hyponatremic patients had an impaired neurohormonal response to orthostasis, lower hepatic and renal plasma flow volumes, elevated liver enzymes, and prerenal azotemia compared with normonatremic patients.

These studies raised the hypothesis that low plasma sodium concentration may be a marker of neurohormonal activation, reflecting the severity of this disease.

Is Hyponatremia a Modifiable Risk Factor?

The relation between changes in plasma sodium levels during hospitalization and mortality in hyponatremic patients admitted for decompensated HF was explored in a post hoc analysis of the ACTIV-CHF trial.[28] Patients with an improvement in plasma sodium concentration (≥2 mEq/L) by the time of discharge had a 60-day mortality rate of 16% compared with 30% in those showing no improvement. After adjustment for other covariates, change in plasma sodium concentration during hospitalization was a significant predictor of mortality 60 days after discharge.[28]

In a retrospective analysis of OPTIME-CHF findings, only 38% of patients in the lowest plasma sodium quartile were able to achieve normalization in plasma sodium concentrations by the time of discharge.[17] The 60-day mortality in this group was 11% compared with 17% in patients who remained persistently hyponatremic at discharge.[17] Importantly, hyponatremia does not appear to improve with the standard treatment currently used in patients with HF during hospitalization. In ESCAPE, persistent hyponatremia was present in most patients who had low plasma sodium levels at baseline.[20]

It appears that improvements in plasma sodium levels during hospitalization in patients with HF may be associated with improved postdischarge mortality; therefore, effective and safe treatments are needed.

Implications for Therapy

Symptomatic patients are usually managed with fluid restriction that results in a negative water balance, increases in plasma osmolality, and increases in plasma sodium. Unfortunately, this therapy is not very effective (may not raise the plasma sodium level by >3 to 4 mEq/L) and is associated with significant discomfort for patients. A combination of hypertonic saline and loop diuretics is often added to fluid restriction, but this more aggressive treatment has been associated with an overly rapid increase in plasma sodium concentration, leading to osmotically induced central nervous system demyelination.[29]

A potential target for hyponatremia therapy is the pituitary hormone arginine vasopressin (AVP), which plays a critical role in regulation of water and electrolyte balance and is inappropriately elevated in patients with HF and hyponatremia.[30,31] V_{1a}-receptors mediate the effects of AVP on vascular tone, whereas V_2-receptors mediate the effects of AVP on plasma osmolality by increasing water resorption in the kidney; therefore, antagonism of those receptors may provide therapeutic benefit for patients with hyponatremia associated with heart failure.[32]

In an early study with a selective V_2-receptor antagonist, tolvaptan, 250 outpatients with HF and signs of congestion were randomized to placebo and 3 different doses of tolvaptan for 25 days.[33] In addition to reducing body weight and lessening edema, tolvaptan therapy normalized plasma sodium concentrations in patients with baseline hyponatremia (Figure 1).[33]

Patients treated with tolvaptan had small increases from baseline in plasma sodium concentrations (<4 mEq/L), whereas small decreases (<1 mEq/L) were seen in placebo-treated patients. A differential response to tolvaptan was observed in patients with normal plasma sodium levels at baseline and in those with hyponatremia. After treatment, normonatremic patients had an acute but transient increase

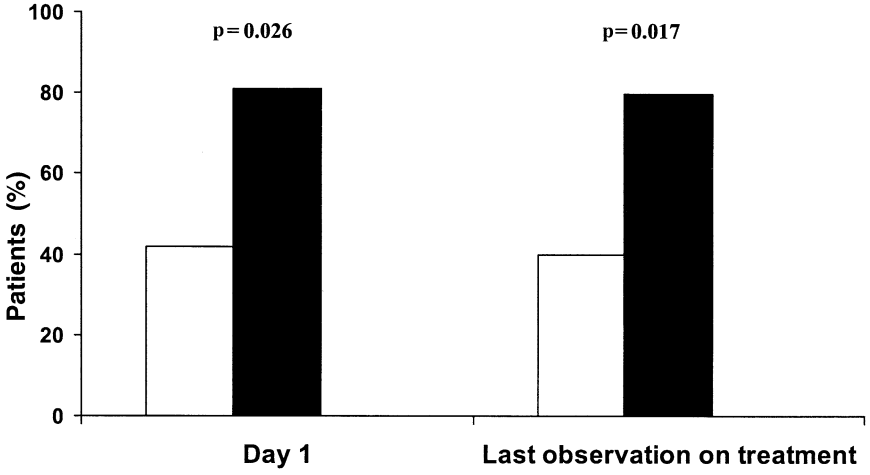

Figure 1. Percentage of hyponatremic patients achieving normalization of plasma sodium concentration at 25 days after treatment with placebo *(open bars)* and tolvaptan *(solid bars)*. (Reprinted with permission from *J Am Coll Cardiol*.[33])

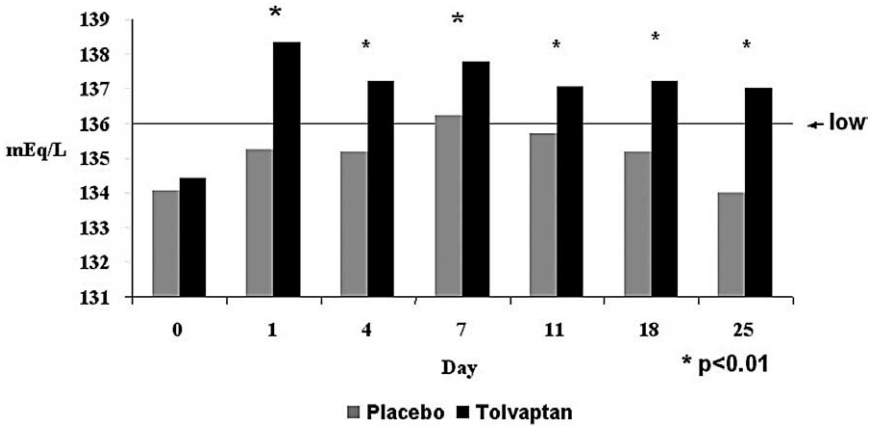

Figure 2. Mean plasma sodium concentrations over time in patients with a baseline serum sodium <136 mEq/L. *p < 0.01.

in plasma sodium levels, with values returning to baseline within 3 weeks of therapy. Patients with hyponatremia had greater increases in plasma sodium levels that remained within the normal range during the study (Figure 2).[34]

The ACTIV-CHF study was a prospective, multicenter, double-blind, placebo-controlled trial conducted in 319 patients who were hospitalized for worsening HF.[18] In the first 24 hours after randomization, patients treated with tolvaptan had small increases from baseline in plasma sodium concentrations, whereas a small decrease was observed in patients receiving placebo. Sixty-eight patients (21%) had hyponatremia at randomization, and the hyponatremic patients in the tolvaptan groups showed a rapid increase, and often normalization, in plasma sodium levels that was sustained throughout the study (Figure 3).[18]

Wong and colleagues[35] investigated the effects of another V_2-receptor antagonist, lixivaptan, at 3 doses (25, 125, and 250 mg twice daily) compared with placebo in 44 patients with hyponatremia and HF, liver cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion. All patients were also treated with fluid restriction of 1,500 mL/day. Lixivaptan produced a significant overall aquaretic response compared with placebo, with significant dose-related increases in net fluid volume, free water clearance, plasma sodium concentration, and serum osmolality.[35]

Recently, results of a randomized, placebo-controlled, multicenter trial of continuous infusions of conivaptan, a combined V_{1a}/V_2-receptor antagonist, have also been reported.[36] The study included hospitalized patients with HF with a plasma sodium concentration between 115 and 130 mEq/L, a fasting blood glucose level <275 mg/dL (15.3 mmol/L) and serum osmolality <290 mOsm/kg of water. Patients were randomized to receive a 20-mg bolus of conivaptan, followed by infusion of conivaptan 40 mg/day for 4 days; a 20-mg bolus of conivaptan, followed by infusion of conivaptan 80 mg/day for 4 days; or placebo.[36] The primary end point of the study was change in plasma sodium concentration from baseline over the duration of the treatment phase. Secondary efficacy end points included (1) time from first dose to an increase in

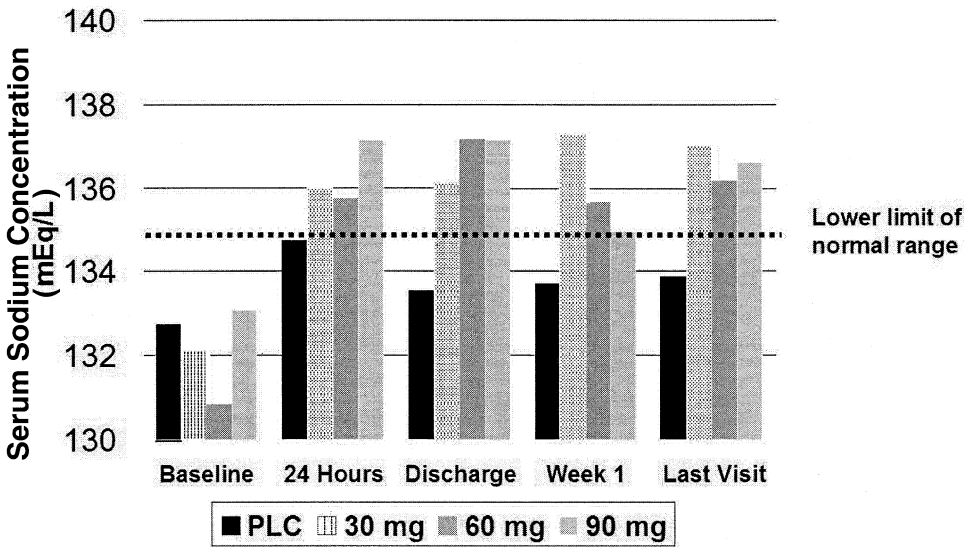

Figure 3. Changes in serum sodium concentrations after treatment among patients with hyponatremia enrolled in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. PLC = placebo. (Reprinted with permission from *JAMA*.[18])

plasma sodium concentration >4 mEq/L from baseline, (2) total time in the treatment phase during which patients had plasma sodium concentrations >4 mEq/L above baseline, (3) change in plasma sodium concentration from baseline to end of treatment, and (4) number of patients achieving an increase in plasma sodium concentration >6 mEq/L, or a normal plasma sodium concentration (>135 mEq/L). Among the 66 patients who completed the study, over the 4-day treatment phase conivaptan 40 and 80 mg/day was significantly more effective than placebo in increasing plasma sodium concentrations.[36] In addition, conivaptan administration resulted in a gradual, dose-related increase in plasma sodium concentration.[36]

The Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) was designed to evaluate the long-term efficacy and safety of oral tolvaptan (30 mg/day) versus placebo in patients hospitalized with decompensated HF and reduced systolic function.[37] End points in this ongoing study are time to all-cause mortality and time to cardiovascular death or hospitalization for HF. The trial will determine the role of vasopressin antagonism in the treatment of HF, and it will be the first study to prospectively test the relation between improvements in plasma sodium levels and outcomes.

Conclusion

Mild hyponatremia is a common electrolyte abnormality encountered in patients hospitalized with HF, and it appears to be an important independent predictor of mortality after discharge. Preliminary data suggest that an improvement in plasma sodium concentration is associated with improved outcomes. Because vasopressin antagonists appear to cause a rapid and sustained normalization in plasma sodium levels in patients with HF and hyponatremia, it is possible that this improvement in plasma sodium concentration translates into improvement in survival. This hypothesis is currently being tested in randomized clinical trials.

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