Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure

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Hyponatremia is an electrolyte disorder commonly encountered in clinical practice, especially in patients with heart failure (HF) with comorbid conditions. Although clear cut-off values for the definition and treatment of hyponatremia are not firmly established, it is often defined as a serum sodium concentration of <136 meq/L. Across all conditions, hyponatremia represents a substantial clinical burden. It has been estimated that hyponatremia is present in 1–2.5% of all hospitalized patients. This rate increases to 15–30% in intensive care units, where hyponatremia is associated with an increased need for mechanical support and a longer length of stay (LOS).

In HF, hyponatremia is characterized by a dilutional effect of excess free water volume. Multiple studies have demonstrated that hyponatremia is an electrolyte disorder commonly encountered in clinical practice, especially in patients with heart failure (HF) with comorbid conditions. Although clear cut-off values for the definition and treatment of hyponatremia are not firmly established, it is often defined as a serum sodium concentration of <136 meq/L. Across all conditions, hyponatremia represents a substantial clinical burden. It has been estimated that hyponatremia is present in 1–2.5% of all hospitalized patients. This rate increases to 15–30% in intensive care units, where hyponatremia is associated with an increased need for mechanical support and a longer length of stay (LOS).

In HF, hyponatremia is characterized by a dilutional effect of excess free water volume. Multiple studies have demonstrated that hyponatremia is associated with an increased risk of hospitalization. In one study, patients with a serum sodium concentration of <130 meq/L had a significantly longer length of stay compared to normonatremic patients. In another study, patients with hyponatremia had a higher risk of death and hospitalization for HF.

Purpose. The effect of serum sodium concentration and tolvaptan treatment on length of stay (LOS) in patients hospitalized with heart failure (HF) was evaluated.

Methods. Data for this study were derived from a large, international, Phase III trial of patients hospitalized for HF. Two distinct post hoc analyses were performed, analyzing the association between serum sodium concentration and hospitalization LOS in normonatremic patients and hyponatremic patients treated with placebo plus standard of care versus tolvaptan. Analysis of covariance models were constructed to adjust for potential variation in care delivery and adjusted for hyponatremia status or treatment.

Results. Patients with a baseline serum sodium concentration of <135 meq/L who received placebo had an adjusted mean LOS that was 3.06 days longer than did normonatremic patients (p < 0.001). More severely hyponatremic patients had an adjusted mean LOS 5.18 days longer than did normonatremic patients (p < 0.001). In an analysis of all hyponatremic patients, those receiving tolvaptan had an adjusted mean LOS that was 1.72 days shorter than those receiving placebo, though this difference was not significant. In more severely hyponatremic patients (serum sodium concentration of <130 meq/L), patients treated with tolvaptan had an adjusted mean LOS 2.12 days shorter than those receiving placebo, but this difference was not significant.

Conclusion. A secondary analysis of a large, international, Phase III trial of patients hospitalized for HF demonstrated that comorbid hyponatremia was associated with a significant increase in hospital LOS. Treatment of hyponatremia with tolvaptan was associated with reductions in LOS that were not significant.

Index terms: Heart failure; Hospitals; Hyponatremia; Tolvaptan; Vasopressin antagonists

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Hypotension is prevalent among individuals hospitalized with HF. For example, in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial, 21% of patients hospitalized for acute decompensated HF had a baseline serum sodium concentration of <136 meq/L. In an analysis of 47,647 patients in a registry of HF admissions across 259 academic and community hospitals, a similar rate was observed.

Since hyponatremia is an independent predictor of prognosis in HF, one goal of treatment in both acute and chronic HF is the prevention of new hyponatremia or the worsening of established hyponatremia. Therapies for the treatment of hyponatremia in HF are generally limited to fluid restriction and, more recently, vasopressin receptor antagonists (i.e., conivaptan and oral tolvaptan), which inhibit the vasopressin V1 receptor on principal cells of the renal collecting duct.

To date, no prospective studies have assessed the effect of treatment of hyponatremia on hospital LOS in patients with hyponatremia. However, the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trials provide a detailed database of patients hospitalized with HF, permitting an examination of the impact of sodium status and potential treatment on LOS. These trials demonstrated that tolvaptan may decrease acute dyspnea and lead to weight loss, though no long-term effects on all-cause mortality or heart-failure-related hospitalization were observed. However, the effect of tolvaptan on LOS has not been previously reported. This is an important issue, as LOS is the primary driver of cost.

The primary objectives of this analysis were to (1) compare inpatient LOS during an index hospitalization for acute decompensated HF between normonatremic and hyponatremic patients and (2) evaluate the effect of tolvaptan versus placebo on LOS in hyponatremic patients hospitalized with HF based on hyponatremia severity.

Methods

Data for this study were derived from patients enrolled in EVEREST, the design of which has been previously described. Briefly, EVEREST was a prospective, international, multicenter, randomized, double-blind, placebo-controlled study conducted at 359 sites between October 2003 and February 2006 and included 4133 patients who were hospitalized with a primary diagnosis of HF. Patients were eligible for the study if they were 18 years of age or older with reduced left ventricular ejection fraction (≤40%), had signs of volume expansion with New York Heart Association (NYHA) functional class III or IV symptoms. Exclusion criteria included but were not limited to a serum creatinine concentration of >3.5 mg/dL (>309 μmol/L), a serum potassium concentration of >5.5 mmol/L, and a supine systolic arterial blood pressure of <90 mm Hg. There were no specific requirements with respect to serum sodium concentration.

Statistical analyses were conducted using SPSS, version 14 (SPSS software, Chicago, IL). Student’s t test and Levene’s test for equality of variances were used to determine statistical significance.
for unadjusted mean LOS differences among groups. An analysis of covariance (ANCOVA) model was constructed to account for regional variation in care delivery attributable to the multinational design of the trials. An ANCOVA model tests whether certain factors have an effect on a continuous outcome variable after removing the variance for which quantitative predictors or covariates account. The inclusion of covariates can increase statistical power because it accounts for some of the variability observed in the outcome.19 For the analysis comparing hyponatremic patients with normonatremic patients, the model was adjusted for hyponatremia status as a factor and for both geographic region and the interaction between hyponatremia status and geographic region as covariates. An ANCOVA model was also constructed for the multivariate analysis of LOS comparing tolvaptan with placebo. The model was adjusted for treatment as a factor and for both geographic region and the interaction between treatment and geographic region as covariates. Statistical significance was assessed using a two-tailed independent sample t test at a significance level of 0.05.

Results

Of 441 hyponatremic patients (serum sodium concentration, <135 meq/L), 225 (51%) were randomized to receive tolvaptan and 216 (49%) were randomized to receive placebo (Figure 1). Patients enrolled from U.S. sites represented 13.5% (n = 557) of all patients in EVEREST and 15.4% (n = 68) of all hyponatremic patients.

Association between serum sodium concentration and index hospitalization LOS in patients receiving placebo. Patients with a baseline serum sodium concentration of <135 meq/L had a significantly longer unadjusted mean LOS during index hospitalization (2.11 days) than did normonatremic patients (p < 0.01) (Table 1). More severely hyponatremic patients (serum sodium concentration of <130 meq/L at baseline) had an unadjusted mean LOS 2.88 days longer than did normonatremic patients, but this difference was not statistically significant (p = 0.17) (Table 1).

After adjusting for geographic region and for the interaction between geographic region and hyponatremia status as covariates, hyponatremic patients had a statistically significant longer adjusted mean LOS across both subgroups (Figure 2). In patients with a serum sodium concentration of <135 meq/L, the observed mean LOS during index hospitalization was 3.06 days longer compared with that of normonatremic patients (p < 0.001); this difference was more pronounced in the subset of patients with a serum sodium concentration of <130 meq/L (5.17 days longer, p < 0.001).

When the analysis was replicated in U.S. trial participants only, patients with a baseline serum sodium concentration of <135 meq/L (n = 68) had a significantly longer unadjusted mean LOS (1.39 days) during index hospitalization than did normonatremic patients (n = 489) (p < 0.05).

Effect of tolvaptan versus placebo on index hospitalization LOS in hyponatremic patients. In patients with
a baseline serum sodium concentration of <135 meq/L, the unadjusted LOS during the index hospitalization did not differ significantly between the tolvaptan and placebo groups (Table 2). In the small proportion of patients with a serum sodium concentration of <130 meq/L, the same lack of significant difference was observed. After adjusting for treatment as a factor and both geographic region and the interaction between treatment and geographic region as covariates, the mean LOS observed in patients with serum sodium concentrations of <135 and <130 meq/L treated with tolvaptan was 1.72 days and 2.12 days shorter than that observed with placebo (p = 0.06 and p = 0.58, respectively) (Figure 3).

Discussion

Hyponatremia is associated with a substantial clinical burden and is an independent predictor of complications and death in patients suffering from a number of conditions, including HF. Various studies have reported that hyponatremia adversely affects morbidity, mortality, and inpatient direct medical costs. Shea et al. reported that in a general hospitalized population, hyponatremia was a significant independent predictor of inpatient costs at both six months (76.4% increase; 95% confidence interval [CI], 55.0–100.7%) and one year (95.6% increase; 95% CI, 73.3–120.8%). In patients with congestive HF, hyponatremia has been demonstrated to be a significant predictor of worsening outcomes, including morbidity and mortality. Additional evidence suggests that the normalization or improvement in serum sodium concentration may have a positive effect on health outcomes. In the ACTIV in CHF trial, a Phase II study of tolvaptan, 21.6% of patients hospitalized for worsening HF had hyponatremia; at discharge, 66.2% had improvements in serum sodium concentrations

Figure 2. Comparison of adjusted mean length of stay between hyponatremic and normonatremic patients after adjustment for geographic region and for the interaction between geographic region and hyponatremia as covariates. Error bars represent the standard error. Na = serum sodium concentration.

Table 1. Comparison of Unadjusted Mean Length of Stay (LOS) Among Hyponatremic and Normonatremic Patients With Placebo

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (meq/L)</th>
<th>n</th>
<th>Unadjusted Mean LOS (days)</th>
<th>Mean LOS Differences (95% CI) (days)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;135</td>
<td>216</td>
<td>10.86</td>
<td>2.11 (0.55 to 3.69)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥135</td>
<td>1789</td>
<td>8.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;135</td>
<td>68</td>
<td>6.96</td>
<td>1.39 (0.12 to 2.67)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>≥135</td>
<td>489</td>
<td>5.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For comparison with patients with serum sodium concentration of ≥135 meq/L. Equal variances were not assumed. CI = confidence interval.

Table 2. Comparison of Unadjusted Mean Length of Stay (LOS) Among Hyponatremic Patients Treated With Tolvaptan or Placebo

<table>
<thead>
<tr>
<th>Serum Sodium Concentration and Treatmenta</th>
<th>n</th>
<th>Unadjusted Mean LOS (days)</th>
<th>Mean LOS Difference (95% CI) (days)b</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;135 meq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>225</td>
<td>9.48</td>
<td>1.38 (–3.16 to 0.41)</td>
<td>0.13</td>
</tr>
<tr>
<td>Placebo</td>
<td>216</td>
<td>10.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130 meq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>32</td>
<td>11.25</td>
<td>0.38 (–5.88 to 5.13)</td>
<td>0.89</td>
</tr>
<tr>
<td>Placebo</td>
<td>48</td>
<td>11.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tolvaptan treatment was 30 mg orally daily.

*For comparison with placebo group. Equal variances were not assumed. CI = confidence interval.
In patients with improved serum sodium concentrations, the mortality rate at 60 days postdischarge was approximately half the comparable figure in patients showing no improvement (11.1% versus 21.7%, respectively), though the study was not powered to show a statistically significant difference for this variable. Change in serum sodium level was a statistically significant predictor of 60-day mortality (hazard ratio, 0.74; p < 0.0185), and patients with an improvement in serum sodium concentration of ≥2 meq/L at discharge had a 60-day mortality rate of 16%, compared with 30% observed in patients with no improvement in serum sodium concentration.

In our analyses, we observed that baseline serum sodium concentrations were significantly associated with overall inpatient LOS among patients with NYHA functional class III or IV HF. Patients receiving treatment with tolvaptan therapy did not have a significant reduction in overall LOS; the failure to achieve statistical significance was likely due to the small sample size. The trial did not have adequate statistical power for these post hoc analyses. Another potential limitation of the current analysis is that EVEREST was conducted multinationaly, and variations in LOS were observed among geographic locations associated with differences in clinical practice. We attempted to adjust for this variation through the use of an ANCOVA model; however, the adjusted mean LOS differences observed were estimations. In addition, other collinear surrogate markers for outcomes in patients with HF, such as ventricular size, level of biomarkers (e.g., brain natriuretic peptide), and frequency of antecedent hospitalizations, were not included as covariates, largely because the multivariate model did not have sufficient power to include additional covariates given the relatively small numbers of study subjects.

Larger observational studies are needed to confirm our findings. Verification that tolvaptan can reduce LOS in patients with HF and hyponatremia, as suggested by our underpowered analysis, might have important economic consequences in light of data demonstrating that LOS is the major cost driver for hospitals.

Conclusion

A secondary analysis of a large, international, Phase III trial of patients hospitalized for HF demonstrated that comorbid hyponatremia was associated with a significant increase in hospital LOS. Treatment of hyponatremia with tolvaptan was associated with reductions in LOS that were not significant.
References