Hyponatremia and Heart Failure

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Disclosures

Dr. Greenberg is a member of the REACH speakers bureau and has received honoraria from Otsuka
Risk Factors for Hyponatremia

**Selected Conditions**
- Heart failure
- Cirrhosis
- SIADH
- Very old or young age
- Adrenal insufficiency
- Hypothyroidism
- Renal dysfunction
- CNS impairment
- Surgery or injury

**Selected Drug Classes**
- Diuretics
- NSAIDs
- Opiate derivatives
- Antidepressants
- Antipsychotics
- Antiepileptic agents
- Anticancer agents
- Antihypertensive agents
- Proton pump inhibitors
# Categorizing Hyponatremia

<table>
<thead>
<tr>
<th>Dilutional</th>
<th>Depletional</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Heart failure</td>
<td>❖ Burns</td>
</tr>
<tr>
<td>❖ SIADH</td>
<td>❖ Vomiting</td>
</tr>
<tr>
<td>❖ Cirrhosis</td>
<td>❖ Diarrhea</td>
</tr>
<tr>
<td>❖ Nephrotic Syndrome</td>
<td>❖ Pancreatitis</td>
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<tr>
<td></td>
<td>❖ Trauma</td>
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</tbody>
</table>

- Total body sodium is normal or increased
- Total body sodium is decreased
Symptoms Associated With Hyponatremia

- Mostly CNS
- Range from mild to life threatening (e.g. headache, confusion, fatigue, nausea and vomiting, seizures, respiratory arrest, brainstem herniation)
- Severity depends on severity of hyponatremia and time course over which it develops
Clinical Manifestations of Mild Chronic Hyponatremia in the Elderly

- Case control study of 122 patients age 72 ± 13 yrs with ‘asymptomatic’ hyponatremia (126 ± 5 mEq/L) compared to 244 matched control.
- 21% of the patients were admitted for fall compared to only 5% of the controls (p<.0001).
- Attention tests: mean response time was 673 sec vs 615 sec, (16% P<.001)
- Total error number increased by 20% (P=.001) comparable to seen after alcohol intake.

Figure 1  Evolution of the “total traveled way” (TTW) by the center of pressure in the dynamic test to walk on the platform 3 stereotyped steps “in tandem,” eyes open, in 3 patients (A, B, C) with mild asymptomatic hyponatremia and after correction. Patients are walking from right to left. Irregular paths of the center of pressure observed in the hyponatremia condition (arrows).
Mild Chronic Hyponatremia is Associated with Falls, Unsteadiness, and Attention Deficits

- CONCLUSIONS: Mild chronic hyponatremia induces a high incidence of falls possibly as the result of marked gait and attention impairments. Treating these patients might prevent a considerable number of hospitalizations.
Prevalence of Hyponatremia in HF

- Hyponatremia (serum sodium < 135 mEq/L) is common in patients hospitalized with HF

![Bar chart showing the prevalence of hyponatremia in different clinical trials.]

Distribution of Baseline Serum Sodium in EVEREST

Hyponatremia

Baseline Serum Sodium Level (mEq/L)

- n=475 (11.5%)
- Severe n=92 (2.2%)
- Mild n=383 (9.3%)

Number of Subjects

Baseline Serum Sodium Level (mEq/L)

Tolvaptan 30 mg
Placebo
Relationship Between Serum [Na$^+$] and In-Hospital Mortality (OPTIMIZE-HF Registry)

Hyponatremia After In-hospital Rx is Associated with Higher 60-day Mortality

**ACTIV-HF= Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure**

Relation of Serum Na Level to Long-Term Outcome After 1st Hospitalization for HFpEF
Hyponatremia Is Associated With Rehospitalization in HF Patients*

- Length of Stay, d:
  - Na <135 mEq/L: 6.4
  - Na ≥135 mEq/L: 5.5

- In-Hospital Mortality, %:
  - Na <135 mEq/L: 6.0
  - Na ≥135 mEq/L: 3.2

- Postdischarge Mortality, %:
  - Na <135 mEq/L: 12.4
  - Na ≥135 mEq/L: 7.1

- Death or Rehospitalization Since Discharge, %:
  - Na <135 mEq/L: 42.5
  - Na ≥135 mEq/L: 34.8

*OPTIMIZE-HF registry data; N=48,612.

Mechanisms of Hyponatremia in HF

- Potent thirst stimulation mediated by low CO and Angiotensin II.
- Diuretics (thiazides, spironolactone, loop diuretics)
- Other drugs (NSAIDs, SSRIs)
- Increased *non-osmotic release* of AVP (2-3 fold increase in hyponatremic patients) due to low CO, decreased RBF, baroreceptor stimulation (mediated by low BP) and other factors.
Neurohormonal Activation in HF
*SOLVD*

**Median Plasma ANF (pg/mL)**

- **Control**
- **Prevention**
- **Treatment**

*P<0.001*  
*P=0.001*

**Median Plasma AVP (pg/mL)**

- **Control**
- **Prevention**
- **Treatment**

*P=0.006*  
*P=0.001*

**Median Plasma Norepinephrine (pg/mL)**

- **Control**
- **Prevention**
- **Treatment**

*P=0.001*  
*P=0.02*

**Median Plasma Renin Activity (pg/mL)**

- **Control**
- **Prevention**
- **Treatment**

*P=0.03*  
*P=0.0003*

*Prevention trial: assessed prevention of HF in asymptomatic patients (n=151);  
†Treatment trial: assessed reduction in mortality in symptomatic patients (n=81).  
Strategies For Correcting Hyponatremia

Add to the numerator

\[ \text{Na}^+_E + \text{K}^+_E \]

Serum [Na+] ~ Body Water

Subtract from the numerator
Treatments for Hyponatremia In HF Patients

- Improve hemodynamics (?)
- Discontinue agents that cause hyponatremia (e.g. NSAIDs, SSRIs)
- Fluid restriction (poorly tolerated and takes time, only 1-2 mEq/L per day)
- Hypertonic saline (safety ?)
- Demeclocycline – variable results/nephrotoxic
- Vasopressin receptor antagonists (i.e. vaptans)
Arginine Vasopressin (AVP) Stimulation and Effects

1. ↑ Osmolality
2. Angiotensin II/NE
3. ↓ Arterial pressure/cardiac volume

V1b-Ant pituitary Pancreas, Adrenal medulla

V1a Receptor (VSMC, cardiomyocytes)

V2 Receptors (collecting ducts)

Vasoconstriction
Myocardial stimulation

Renal H₂O reabsorption

1. ↓ Osmolality
2. Natriuretic peptides
3. ↑ Arterial pressure/cardiac volume

Vasopressin Effector Mechanisms

Vasopressin effects mediated by:

- $V_2$ receptors (renal tubules)
  - Water retention
- $V_{1a}$ receptors (blood vessels, myocardium)
  - Peripheral and coronary vasoconstriction
Vasopressin Antagonists in Heart Failure

• Conivaptan—dual $V_1/V_2$ receptor antagonist
• Lixivaptan—$V_2$ receptor antagonist $>>>V_1$
• Tolvaptan—$V_2$ receptor antagonist $>>V_1$
Vaptans: Mechanisms of Action

1. Vasopressin binds to membrane receptor.
2. Receptor activates cAMP second messenger system.
3. Cell inserts AQP2 water pores into apical membrane.
4. Water is absorbed by osmosis into the blood.
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SALT Studies

• 2 multicenter, randomized, double blind, placebo-controlled trials.

• Objective: to evaluate the efficacy and safety of outpatient tolvaptan administration in pts with euvolumic or hypervolumic hyponatremia of diverse causes.

• Evaluate of QOL on day 30 using the SF-12 Health Survey.

Schrier R et al NEJM 2006:355;2099
SALT 1 and 2: Mean Sodium Concentration Over Time


*P* < .001 for tolvaptan vs. placebo; tolvaptan was discontinued on day 30

SALT-2 and SALT-2=Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2
Effects of Tolvaptan in the SALT Trials

- No effect of the study drug on physical component of the SF-12 Health survey.
- There was however a significant effect on the mental component (P=0.02 for both studies)

Indications for Tolvaptan in HF Patients With Hyponatremia

- Dilutional hyponatremia with serum Na+ < 125 mEq/mL
- Symptomatic patients with Na+ with serum Na+ between 125 and 135 mEq/mL that have not responded to fluid restriction
Effect of Single Dose Conivaptan on Urine Output in Advanced HF

Change in Urine Output (UO) 0-4 h

Change UO (mL/h) vs Time (h)

- Placebo
- 10 mg
- 20 mg
- 40 mg

* P < .005

Effect of Single Dose Conivaptan on PAWP in Advanced Heart Failure

Peak Change in PCWP at 3-6 Hours

<table>
<thead>
<tr>
<th>Conivaptan</th>
<th>Change PCWP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=38)</td>
<td>-2.6</td>
</tr>
<tr>
<td>10 mg (n=37)</td>
<td>-3.7</td>
</tr>
<tr>
<td>20 mg (n=32)</td>
<td>-5.4</td>
</tr>
<tr>
<td>40 mg (n=35)</td>
<td>-4.6</td>
</tr>
</tbody>
</table>

* $P < .05$
** $P < .01$

EVEREST: 3 Trials in One

OBJECTIVE:
Evaluate tolvaptan effects on signs/symptoms in-hospital

Separate Sites

Short-term Clinical Status Trail A

Short-term Clinical Status Trail B

Long-term Outcome Trial
Long-term drug administration

OBJECTIVE
Evaluate tolvaptan effects on morbidity / mortality
EVEREST Entry Criteria

Inclusions

• Hospitalization for HF <48hrs
• Evidence of hyponatremia not required*
• LVEF ≤40%
• Fluid overload; ≥2 of the following:
  • Jugular venous distention
  • Pitting edema (>1+)
  • Dyspnea

Exclusions

• Recent or planned revascularization or device implant
• STEMI during hospitalization
• Systolic BP <90 mm Hg
• Creat >3.5 mg%; K >5.5 mEq/L; Hgb <9 g%
Composite Components (Day 7 or Discharge)

Change in Body Weight

<table>
<thead>
<tr>
<th>Change in Body Weight</th>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional weight loss</td>
<td>0.6 kg</td>
<td>0.9 kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=997</td>
<td>n=1007</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Change in Global Clinical Status

<table>
<thead>
<tr>
<th>Change in Global Clinical Status</th>
<th>Trial A</th>
<th>Trial B</th>
</tr>
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<td>0.6 kg</td>
<td>0.9 kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=903</td>
<td>n=910</td>
</tr>
<tr>
<td>P=0.51</td>
<td>P=0.52</td>
</tr>
</tbody>
</table>

No difference in GCS improvement
Physician-Assessed Signs and Symptoms

(% Patients with Improvement)

**Physician-Assessed Signs and Symptoms**

- **Dyspnea**
  - *P < 0.05 for all days compared to Placebo

- **Fatigue**

- **Orthopnea**
  - *P < 0.05 for all days compared to Placebo

- **Edema**
  - *P < 0.05 for all days compared to Placebo
EVEREST: Primary End Points

**All-Cause Mortality**
- HR 0.98; 95%CI (.87-1.11)
- Meets criteria for non-inferiority

**CV Mortality or HF Hospitalization**
- HR 1.04; 95%CI (.95-1.14)
Adjudicated CV Mortality/Morbidity

**EVEREST Trial: Patients with HF and Hyponatremia**

**Subjects with Baseline Sodium ≥130 mEq/L (ITT Population)**

- **Tolvaptan**
- **Placebo**

Hazard Ratio: 0.603
95% CI Limits: 0.372, 0.979

**Subjects with Baseline Sodium <130 mEq/L (ITT Population)**

(p<0.05)
Hazard Ratio: 1.065
95% CI Limits: 0.973, 1.165

Overall CV Mortality/Morbidity (ITT) HR 1.04; 95%CI (.95-1.14)

DATA on File: Protocols 156-02-235 and 156-03-238.
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Tolvaptan (n=2072)</th>
<th>Placebo (n=2061)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>133 (6.4)</td>
<td>140 (6.8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypotension</td>
<td>233 (11.3)</td>
<td>226 (11.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>123 (6.0)</td>
<td>118 (5.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>116 (5.6)</td>
<td>122 (5.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>174 (8.4)</td>
<td>44 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thirst</td>
<td>331 (16.0)</td>
<td>43 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>161 (7.8)</td>
<td>136 (6.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>166 (8.0)</td>
<td>202 (9.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>35 (1.7)</td>
<td>10 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>21 (1.0)</td>
<td>39 (1.9)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Changes in Renal Function

**BUN (mg/dL)**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7 or Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>1987</td>
</tr>
<tr>
<td>1940</td>
<td>1951</td>
</tr>
</tbody>
</table>

**Serum Cr (mg/dL)**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7 or Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1912</td>
<td>1925</td>
</tr>
<tr>
<td>1864</td>
<td>1886</td>
</tr>
</tbody>
</table>

**Inpatient**

**Outpatient**

**TLV PLC**

- Day 1
- Day 7 or Discharge
- After Discharge (wk)
Common Side Effects With Tolvaptan

- Thirst
- Polydipsia/polyuria
- Dry mouth
- Frequent daytime urination
Uncommon But Serious Side Effects With Vaptans

- Central pontine myelinolysis – caused by too rapid increase in Na+ concentration (>12mEq/L over 24 hours).
Case Presentation

• 80 yo female with long-standing HF (EF 32%) admitted with symptoms related to worsening volume overload. She also complains of severe nausea.

• No obvious ‘trigger’ for decompensation.

• Patient has been compliment with regimen of bumetanide 4 mg bid, lisinopril 10 mg bid, carvedilol 12.5 mg bid and spironolactone 12.5 mg qd.
80 Year Old Female With Worsening HF

- Examination showed the patient to be mildly uncomfortable with BP 110/72 and P 84.
- JVP was to the angle of the jaw when she was sitting up and she had bibasilar rales.
- Extremities were warm with 1+ edema.
- Labs – Cr 1.47 mg/dL, Na+ 114 mEq/mL
Hospital Course

- Initial treatment consisted of IV bumetanide and fluid restriction.
- On hosp day 1 she diuresed 1.2 litres and was less SOB. JVP was slightly reduced.
- Na+ was 123 mEq/mL and Cr was stable.
- On hosp day 2 she diuresed only 400 ml. JVP was unchanged. Na+ was 121 mEq/mL and Cr was 1.61 mEq/mL.
Treatment

• A bumetanide drip at 1 mg/h was started and tolvaptan 15 mg daily was added to her regimen.

• On Day 3 she diuresed 1.7 liters and Na⁺ was 124mEq/mL.

• Over the next several days she diuresed 3 liters and Na⁺ increased to 131 mEq/mL.

• Patient felt considerably better. She was switched to oral diuretics.

• On day 5 tolvaptan was discontinued. Sodium remained in the 130 mEq/mL range and she was discharged with close followup.
Management Issues

- Fall precautions during early period in hospital
- Electrolytes obtained 4x/day for first 2 days after tolvaptan started then back to 2x/day.
Clinical Implications: Approaches to Managing Patients with Hyponatremia

- Hyponatremia is common in patients with decompensated HF and is associated with cognitive and neuromuscular impairment and increased mortality.

- Vaptans increase Na+ levels in congested hyponatremic patients.

- Vaptans can improve cognitive function, enhance diuresis and improve hemodynamics.

- Vaptans are well tolerated with low SE profile.

- Effects of vaptans on survival and other outcomes in hyponatremic heart failure patients are uncertain.
Clinical Implications: Approaches to Managing Patients with Hyponatremia

- Vaptans are a useful adjunct to therapy in decompensated heart failure patients with serum Na+ below 125 mEq/mL and in symptomatic patients with Na+ levels between 125 – 135 mEq/mL.