Hyponatremia and Hypovolemia in Heart failure

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Zagazig University

Hyponatremia; definition

Serum Na < 135 mmol/L

Lancet 1998;352:220–228
Hyponatremia; Incidence

- 21% [ACTIV in CHF] JAMA. 2004
- 27% [OPTIME-CHF] Circulation. 2005
- 20% [OTIMIZE-HF] Eur Heart J. 2007

Hyponatremia; Symptoms and signs

- None
- Headache
- Lethargy
- Dizziness and ataxia
- Mild confusion
- Psychosis
- Seizures
- Coma

CMAJ 2004;170(3):365-9
Causes and characteristics of hyponatremia

The vicious circle of CHF

Myocardial Injury

\[ \text{Decreased ventricular performance} \]

Ventricular pre- and afterload

Myocardial hypertrophy & Ischemia

\[ \downarrow \text{COP} \]

Systemic VC

Na & H₂O retention

Neurohormonal responses

Symp. ++

RAAS

AVP; Non osmotic release
SOLVD Trial

Control (1.4-2.3)  Prevention (1.7-3.0)  Treatment (2.3-4.4)

P=0.006  P=0.0001

Median Plasma AVP

Circulation 1990;82:1724-1729

Osmolality
Major stimuli
↓ Blood volume (BLP)
Become Major stimulus in oedematous states

Angiotensin II
catecholamines

Am Heart J. 2003;146:9
AVP Receptors

V1a

VASCULAR SMOOTH MUSCLE CELL

VC

Coronary VC Myocyte Hypertrophy

• ↑Afterload and wall stress
• LVH
• Ischemia
• ↑Preload, hyponatremia, edema

V1a

HEART

H2O Retention

V2

DISTAL TUBULES

AVP Role in H2O Balance and Hyponatremia

Circulation 2008;118;410-421

Elevated AVP impaire solute-free water excretion in HF
Hyponatremia and prognosis In HF

- Hyponatremia (even mild hyponatremia) in Pt with HF exacerbation portends a worse prognosis.

Characteristics of an Ideal Treatment for DHF

- Early symptom relief
- Promotes diuresis (clear water vs electrolytes)
- Provides VD (venous and arterial)
- Improves end-organ function (eg, renal function)
- Does not exacerbate arrhythmias or ischemia
- Does not interfere with other important therapies (eg, β-blockers)
- Length of hospital/ICU stay
- 30 day readmission and mortality
- Cost effective

Am Heart J. 2003;145:S3-S17.
Hyponatraemia as a marker for renin heart failure.

Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure

WH Lee and M Packer

Circulation 1986;73:257-267
Changes in Brain Natriuretic Peptide Levels and Bioelectrical Impedance Measurements After Treatment With High-Dose Furosemide and Hypertonic Saline Solution Versus High-Dose Furosemide Alone in Refractory Congestive Heart Failure
A Double-Blind Study

<table>
<thead>
<tr>
<th>Furosemide Without HSS</th>
<th>Furosemide With HSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry</strong></td>
<td><strong>6 Days</strong></td>
</tr>
<tr>
<td>Patient number</td>
<td>46</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>74.5 ± 6</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146 ± 22</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>82 ± 14</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>83 ± 15</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>30.2 ± 5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75.8 ± 15</td>
</tr>
<tr>
<td>Urine output (ml/24 h)</td>
<td>425 ± 129</td>
</tr>
<tr>
<td>Serum Na (mEq/L)</td>
<td>134.9 ± 7</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>4.3 ± 0.6</td>
</tr>
<tr>
<td>Urea N (mg/dL)</td>
<td>54.3 ± 12.4</td>
</tr>
<tr>
<td>Creatine K (mg/dL)</td>
<td>91 ± 21</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>56.1 ± 3.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.51 ± 0.05</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.6 ± 2.1</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>10.5 ± 2.6</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>8.1 ± 2.4</td>
</tr>
</tbody>
</table>
Treatment Challenges

More than 50% of Patients Have Little or No Weight Loss During Hospitalization

Current treatment options
- Loop diuretics
- IV inotropes
- Nitrates
- Nesiritide

AVP Antagonism

- AVP antagonism at V2 receptor → dose-related ↑solute-free H2O excretion
- ↑ Serum Na
- ↑ Serum osmolality

In HF with Hyponatremia

JACC. 2006;47:1615–1621

Loop Diuretic & Hyponatremia

Hyponatremia with volume overload and HF creates substantial management challenges.

TTT of the volume-overload with loop diuretics can exacerbate the free H2O excess →
Maintaining or even worsening magnitude of hyponatremia.

Circulation 2008;118;410-421
Loop diuretic & Renal function

- Pt with DHF, higher-dose loop diuretic \( \rightarrow \) worsening renal function.

\[ \text{Am J Cardiol. 2005;96:19L-23L} \]

V2 Blocker & Renal function

- V2 blocker increase urine output and RBF.
- In comparison, Loop diuretic increase urine output to a comparable degree but at the expense of
  - Electrolyte excretion (Na and K)
  - Renal blood flow

\[ \text{Am J Physiol Renal Physiol. 2006} \]
V2 Blocker and RAAS

- Unlike Loop diuretic, doesn’t activate RAAS.
- With V2 blocker, Solute-free losses from:
  - ICF (2/3)
  - ECF (1/3)
- Loop diuretics: Na loss exclusively from:
  - ECF

ECF Less Depleted

ECF Depletion

+++ RAAS


Properties of Vasopressin Antagonists Tested in Human Trials

<table>
<thead>
<tr>
<th>Vasopressin Antagonist</th>
<th>Tolvaptan (OPC-41061)*</th>
<th>Lanvaptan (OP-959)*</th>
<th>Conivaptan (VM-861)*</th>
<th>Satiavataplan (SR-121463)*</th>
<th>Micerevant (OPC-31204)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>V2</td>
<td>V2</td>
<td>V1a/V2</td>
<td>V2</td>
<td>V1a/V2</td>
</tr>
<tr>
<td>Selectivity</td>
<td>2:1</td>
<td>10:1</td>
<td>10:1</td>
<td>112:1</td>
<td>10:1</td>
</tr>
<tr>
<td>Vasopressin analogs</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous</td>
<td>Oral</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Administration route</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous</td>
<td>Oral</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>6-8</td>
<td>7-10</td>
<td>14-17</td>
<td>14-17</td>
<td>1-8</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4/CYP2C9)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
</tr>
<tr>
<td>Clinical development</td>
<td>Hyponatremia, decompensated HF, POCD</td>
<td>Hyponatremia, decompensated HF, with hyponatremia</td>
<td>Hyponatremia, decompensated HF</td>
<td>Hyponatremia, HF, cirrhosis (propranolol of efficacy)</td>
<td>Hyponatremia (only SARI)</td>
</tr>
</tbody>
</table>

Circulation 2008;118;410-421
### AVP Receptor Antagonists in HF With Hyponatremia: Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Design</th>
<th>Drug</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chugh et al. subgroup analysis&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Placebo-controlled, double blind, multicenter (20, 45, or 60 mg orally daily for 26 d)</td>
<td>Tolvaptan</td>
<td>HF patients regardless of LVEF</td>
<td>Daily weight</td>
<td>Normalization of serum sodium by day 1 and maintained</td>
</tr>
<tr>
<td></td>
<td>Subgroup of 28% (of 304 total) with hyponatremia (Na&lt;sub&gt; &lt; &lt;/sub&gt;130 mEq/L) at baseline</td>
<td>...</td>
<td>...</td>
<td>Urine volume (day 5), serum sodium</td>
<td>Decrease in body weight and serum increased urinary volume</td>
</tr>
</tbody>
</table>

#### ACTIV in HF (subgroup analysis)<sup>31</sup>

| | Multicenter, placebo controlled, double blind (20, 45, or 60 mg orally daily up to 60 d) | Tolvaptan | Decompensated HF with LVEF <40% and 2 clinical signs of volume overload | Secondary end point: sodium levels | In subgroup with hyponatremia, sodium levels increased and often normalized |
| | Subgroup: 16% (of 304 total) with hyponatremia (Na < 130 mEq/L) | ... | ... | ... | ... |

#### EVEREST (subgroup analysis)<sup>44</sup>

| | Multicenter, placebo controlled, double blind, single dose (60 mg orally daily for up to 60 d) | Tolvaptan | Decompensated HF patients with LVEF <40% | All-cause mortality | In subgroup with hyponatremia, no effect on mortality or HF morbidity |
| | Subgroup: 23% (of 4153 total) with hyponatremia (Na < 130 mEq/L) | ... | ... | First occurrence of cardiovascular mortality or heart failure hospitalization | Significant increase in mean serum sodium |

#### BALANCE<sup>51</sup>

| | Multicenter, placebo controlled, double-blind | Lisinopril | Decompensated HF with hyponatremia | ... | Pending |

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**The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF trial)**

<table>
<thead>
<tr>
<th>V&lt;sub&gt;1a&lt;/sub&gt;</th>
<th>BL.V. Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Renal tubules</td>
</tr>
</tbody>
</table>

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### JAMA®

*Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure: A Randomized Controlled Trial*

Mihai Gheorghiade; Wendy A. Gattis; Christopher M. O'Connor; et al.

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**14**
Vasopressin Antagonist for Heart Failure: ACTIV in CHF Trial

Mean Body Weight Changes During Hospitalization

24 Hours

Discharge

** P<0.05 vs Placebo

-5
-4
-3
-2
-1
0

Kg

Placebo  Tolvaptan 30 mg  Tolvaptan 60 mg  Tolvaptan 90 mg

Mean 24-Hour Urine Volumes at Day 1 and at Hospital Discharge

P<0.001
Signs and Symptoms of Heart Failure at Day 1 and at Hospital Discharge

Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Telapton 30 mg (n = 76)</th>
<th>Telapton 60 mg (n = 84)</th>
<th>Telapton 90 mg (n = 77)</th>
<th>Combined (n = 239)</th>
<th>Placebo (n = 86)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by 60 days</td>
<td>3 (9.8)</td>
<td>8 (11.5)</td>
<td>2 (5.5)</td>
<td>13 (5.4)</td>
<td>7 (8.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>0</td>
<td>1 (1.2)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>2 (2.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>14 (18.4)</td>
<td>17 (20.5)</td>
<td>14 (18.4)</td>
<td>44 (18.4)</td>
<td>14 (17.2)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>20 (25.6)</td>
<td>22 (26.5)</td>
<td>15 (19.4)</td>
<td>51 (21.7)</td>
<td>22 (25.5)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Data are No. (%). Defined as death, rehospitalization, or unscheduled visits for heart failure.
Vasopressin Antagonist for Heart Failure: ACTIV in CHF Trial

60-Day All-cause Mortality

- Placebo
- Tolvaptan

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (%)</th>
<th>Tolvaptan (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8.7 (20%)</td>
<td>5.4 (22%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia (Na+ &lt;135 mEq/L)</td>
<td>18.7 (37%)</td>
<td>13.2 (46%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>↑ BUN (&gt; 29 mg/dL)</td>
<td>20 (37%)</td>
<td>9.1 (46%)</td>
<td></td>
</tr>
<tr>
<td>Congestion*</td>
<td>17.8 (51%)</td>
<td>5.5 (68%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Edema, Dyspnea, and JVD at baseline

**ACTIV**

Tolvaptan ↑ net fluid loss → ↓ body weight more effectively than standard therapy alone in Pt with HF.

No effect on Bl P, HR, elect. levels, or renal function.

Tolvaptan improved serum Na levels in pt with hyponatremia.

Although Tolvaptan did not reduce the rate of worsening HF after discharge, post hoc analysis suggested that mortality might be reduced in high risk ptients treated with tolvaptan.
Efficacy of Vasopressin antagonism in heart failure: outcome study with Tolvaptan (EVEREST)

\[
\begin{array}{|c|c|}
\hline
V_{1a} & BL.V. \\ 
& Myocardium \\
\hline
V_{2} & Renal tubules \\
\hline
\end{array}
\]

Tolvaptan

EVEREST: 3 Trials in One

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

Separate Sites

Short-term Clinical Status Trial A
Short-term Clinical Status Trial B

Long-term Outcome Trial
Long-term drug administration

OBJECTIVE
Evaluate tolvaptan effects on morbidity / mortality
Composite Components (Day 7 or Discharge)

Change in Body Weight

- Additional weight loss
  - Tolvaptan: 0.6 kg
  - Placebo: 0.9 kg

Change in Global Clinical Status

- No difference in GCS improvement

Secondary Endpoints: Day 1

Δ in BW (kg)

- Trial A
  - Tolvaptan: -1.7 ± 1.8
  - Placebo: -1.0 ± 1.8
- Trial B
  - Tolvaptan: -1.8 ± 2.0
  - Placebo: -0.9 ± 1.9

Δ in Dyspnea (% of pts with baseline dyspnea)

- Improved
  - Trial A
    - Tolvaptan: 16
    - Placebo: 24
  - Trial B
    - Tolvaptan: 14
    - Placebo: 26
- Markedly better
- Moderately better
- Minimally better
- Worse

Both trials P<0.001
Secondary Endpoint: Day 7 or DC
Δ in Edema Score (% of patients with baseline edema)

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P=0.07</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Tolvaptan (n=772)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=790)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolvaptan (n=828)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=805)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-4        -3        -2        -1        0        1        2

Improved

-4        -3        -2        -1        0        1        2

worsened

Physician-assessed Signs and Symptoms (% Patients with Improvement)

Tolvaptan

Placebo

* P<0.05
Outcome Trial 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)
Changes in Body Weight and Serum Sodium by Visit

<table>
<thead>
<tr>
<th></th>
<th>Inpatient</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
</tr>
<tr>
<td>Serum Na⁺ (mEq/L) (baseline &lt;134 mEq/L)</td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th>Event</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>
EVERSET

1. In well-treated patients hospitalized with HF, oral tolvaptan, 30 mg daily, facilitates management of volume overload with
   - Early and sustained weight reduction
   - Improvement in dyspnea (d1) and edema (d7)
   - No effect on global clinical status (VAS) at d7/DC
   - Normalization of serum sodium
   - Maintenance of renal function.

2. Long-term treatment had no effect on long-term mortality or HF morbidity.

3. Tolvaptan achieved short-term symptom benefit with a well-defined and acceptable long-term safety profile.

Conviptan in HF

- Dual V1a/V2 receptor antagonist

**PCWP**

**Urine Output**

*Circulation 2001;104:2417-23.*
Conivaptan in Pt With HF

- Combined $V_{1a}/V_2$-receptor antagonism
- In HF, IV conivaptan resulted in
  - Significant reductions in PCWP and right atrial pressure (RAP)
  - No change in CI, HR, MAP, PVR, SVR
  - Dose-dependent increase in urine output
  - “Aquaresis” without solute loss and increase in serum sodium concentrations

THANK YOU