Learning Objectives

- Describe the underlying pathophysiology, risk factors, and risk stratification of hospitalized patients with hyponatremia
- Identify the mechanisms in which hyponatremia complicates the management of chronic medical conditions
- Assess the pharmacist’s role and current treatment options for hyponatremia in the hospital setting.
- Examine the role of vasopressin receptor antagonists in the management of hyponatremia in the hospitalized patient

Faculty Disclosures

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PLEASE ANSWER THE HYPONATREMIA PRE-ACTIVITY TEST QUESTIONS

Question 1
How confident are you in your ability to summarize the Hyponatremia Treatment Guidelines: 2007 Expert Panel Recommendations?

1. Not at all confident
2. Somewhat confident
3. Confident
4. Very Confident
5. Extremely Confident

Question 2
Compared with standard diuretics, vasopressin receptor antagonists act at a different site of the nephron to induce selective water diuresis without affecting sodium and potassium excretion.

A. True
B. False
Patient Case: Asymptomatic Hyponatremia

- 75-yo female, stable CHF and type 2 DM
- Fell while coming down the stairs in her house, now severe leg pain, pleuritic chest pain, SOB
- ER: left hip fracture, multiple rib fractures, small pleural effusions bilaterally, no pneumothorax
- Admitted to ICU for monitoring, physical exam: patient is awake and oriented; blood pressure is 130/80; no focal neurological deficits; bibasilar rales; point tenderness over rib cage

Patient Case: Asymptomatic Hyponatremia

Labs:

- Na = 128, K = 3.4, Cl = 104, HCO3 = 24
- glucose = 185, BUN = 20, Cr = 1.3
- Hct = 36
- Posm = 275, Uosm = 350, UNa+ = 60
- O2 sat = 90% room air

Question 3

Is this patient a candidate for vasopressin antagonist therapy for hyponatremia?

A. Yes
B. No
Question 4

How common is hyponatremia in your institution or practice? You see hyponatremia in:

A. Less than 5% of patients
B. 5-10% of patients
C. 10-15% of patients
D. More than 10% of patients

Question 5

According to data from the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT 1 and 2) serum sodium concentrations ________ in the tolvaptan group when compared to the placebo group during the first 4 days and after the full 30 days of therapy.

A. Did not change
B. Increased
C. Decreased
D. Were equal

Question 6

Of patients treated for hyponatremia, what percentage are initially treated as inpatients?

A. 10% - 25%
B. 26% - 43%
C. 44% - 54%
D. 55%–63%
Question 7
Which of the following non-peptide AVP receptor antagonists is available as an intravenous (IV) formulation:
A. Tolvaptan
B. Conivaptan
C. Lixivaptan
D. Satavaptan

Hyponatremia
- Most common electrolyte abnormality
- Associated with many systemic diseases
  - Major: dilution of extracellular fluid
  - Minor: total body losses of sodium
- Acute vs. Chronic
  - Often duration is difficult to determine

Hyponatremia can be caused by dilution from retained water, or by depletion from electrolyte losses in excess of water
Role of Vasopressin

- Vasopressin = ADH = antidiuretic hormone
- Physiologic sodium/water balance
  - Thirst: stimulated by rise in osmolality
    • Osmoreceptors
  - Water excretion: regulated by vasopressin
    • Osmoreceptors
      - ↑ Osmolality = ↑ vasopressin secretion = ↑ H2O reabsorption
      - ↓ Osmolality = ↓ vasopressin secretion = ↓ H2O reabsorption

AVP regulation of water reabsorption from renal tubular cells

- AVP activates V2 receptors
- ATP binding to Gs protein
- cAMP stimulates AQP2 insertion
- Water reabsorption in collecting duct cells
Classification: Osmolality

- Hypotonic hyponatremia
  - Sodium directly related to osmolality
  - Most cases

- Isotonic/Hypertonic hyponatremia
  - Pseudohyponatremia
  - Non-sodium solutes increase osmolality
    - Glucose
    - ↑ osmolality → fluid shifts → dilution of sodium

Classification: Volume Status

- Hyponatremia
  - Hypovolemic
    - Na+ Loss
      - Diuretics
      - Mineralocorticoid Deficiency
      - Glucosuria
      - Ketonuria
      - Vomiting
      - Diarrhea
  - Euvolemic
    - Non-Physiologic Release of ADH
      - SIADH
      - SIADH Heart Failure
      - SIADH Liver Disease
      - SIADH Kidney Disease
  - Hypervolemic

Drug-Related Causes

- Sodium Loss
  - Diuretics

- ↑ Vasopressin/ADH effects
  - Antipsychotics
  - Antidepressants
  - DDAVP
  - Oxytocin
Risk Stratification

- **Acute vs. Chronic**
  - Acute = less than 48 hours in duration
    - Concerned about neurologic sequelae
    - Osmotic differential between brain and blood
    - Brain swelling
  - Chronic = greater than 48 hours in duration
    - Symptoms may be more modest
    - Brain has time to adapt

- **Duration of hyponatremia**
  - How aggressive?
  - How fast?

Symptomatic Hyponatremia: Neurological Manifestations

- Headache
- Irritability
- Nausea/Vomiting
- Mental Slowing
- Confusion/Delirium
- Disorientation
- Stupor/Coma
- Convulsions
- Respiratory Arrest

Symptoms Associated with Chronic Hyponatremia

- Malaise/Lethargy: 109 (49%)
- Dizzy Spells: 104 (47%)
- Vomiting: 77 (35%)
- Confusion/Obtundation: 39 (17%)
- Falls: 37 (17%)
- Headache: 13 (6%)
- Seizures: 2 (0.9%)

223/223 resolved symptoms with correction of [Na+] via cessation of thiazide treatment
Increased Risk of Falls with “Asymptomatic” Hyponatremia

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Falls</th>
<th>Odds Ratio</th>
<th>Adjusted Odds Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Asymptomatic” Chronic Hyponatremia</td>
<td>122</td>
<td>21.3%</td>
<td>9.45 (2.64-34.09) p &lt; .001</td>
<td>67.43 (7.48-607.42) p &lt; .001</td>
</tr>
<tr>
<td>Normonatremic controls</td>
<td>244</td>
<td>5.35%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>


Sodium and the Brain

Na⁺ moves from high concentrations to low
Water follows Na⁺

Time-dependent

BRAIN EDEMA

Reductions of Brain Organic Osmolytes after 14 days of Sustained Hyponatremia

The hyponatremic brain is NOT a normal brain, but rather represents a state of allostasis as a result of solute losses


*P < 0.01 compared to normonatremic control rats.
Acute vs. Chronic and the Brain

- **Acute hyponatremia**
  - Rapid onset
  - Greater likelihood of rapid fluid shifts and brain edema

- **Chronic hyponatremia**
  - Insidious onset
  - Less likelihood for brain edema
  - Time for compensatory increases in organic osmolytes

Sodium and the Brain

\[ \text{Na}^+ \text{ moves from high concentrations to low} \]

Water follows \( \text{Na}^+ \)

Implications for treatment

Rapid fluid shifts out of the brain: OSMOTIC DEMYELINATION

How Aggressive? How Fast?

- **LEVEL 3 - SEVERE SYMPTOMS:**
  - vomiting, seizures, obtundation, respiratory distress, coma
  - **Emergency! Correct RAPIDLY**

- **LEVEL 2 - MODERATE SYMPTOMS:**
  - nausea, confusion, disorientation, altered mental status

- **LEVEL 1 - NO OR MINIMAL SYMPTOMS:**
  - headache, irritability, inability to concentrate, altered mood, depression
  - **OK to correct more slowly**
Hyponatremia and Heart Failure

Implications of Hyponatremia

Heart failure
- There are an estimated 7 million Americans with HF (2% of US population).
- Hyponatremia is one of the newer and emerging risk factors for an adverse prognosis in chronic heart failure.
- Inadequate release of vasopressin may result in excess fluid retention and hyponatremia.

In-hospital mortality risk groups according to the ADHERE risk stratification

- Age > 78 years → 1.88 (1.74 – 2.04)
- BUN > 42 → 3.34 (3.08 – 3.62)
- SCr > 3.2 → 1.99 (1.78 – 2.24)
- SBP ≤ 115 → 3.09 (2.85 – 3.35)
- DBP ≤ 55 → 2.87 (2.62 – 3.14)
- Serum Na+ < 134 → 2.26 (2.08 – 2.47)
- HR > 84 → 1.20 (1.11 – 1.30)
- Dyspnea at Rest → 1.57 (1.45 – 1.70)

Abraham WT, et al. JACC 2005;46:57-64
Hyponatremia and Liver Disease

Implications of Hyponatremia

Liver Disease
- Associated with poor prognosis & reduced survival
- Impairs the management of ascites
- Predisposes to hepatic encephalopathy
- Impairs quality of life

Pathogenesis of Hyponatremia in Cirrhosis

- Sinusoidal portal hypertension
- Severe liver dysfunction
- Systemic arterial vasodilation
- Hyperdynamic circulation
- Activation of RAAS & SNS
- Non-osmotic release of vasopressin
- Severe renal Na retention proximal > distal tubular
- Water retention follows Na retention

When water retention > Na retention, hyponatremia develops
Distribution of serum sodium in patients with liver cirrhosis & ascites (n=983)

Serum Sodium and Mortality
Liver Transplant candidates in the VA system, 97-03 (n=507)
- Hepatitis C (68%), EtOH (67%)
- MELD 16.2 ± 6.7
- Hyponatremia (<130 mEq/L): 31%
- Persistent Ascites/Hydrothorax: 38%

• Predictors of 6-month mortality

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>1.25 (1.16-1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Na &lt; 135 mEq/L</td>
<td>2.76 (1.31-5.81)</td>
<td>0.008</td>
</tr>
<tr>
<td>Persistent Ascites</td>
<td>2.72 (1.31-5.71)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH): Essential Criteria

- True plasma hypoosmolality
- Urine concentration inappropriate for plasma osmolality ($U_{\text{osm}} > 100 \text{ mOsm/kg H}_2\text{O}$)
- Clinical euvolemia, no diuretic therapy
- Absent renal sodium conservation ($U_{\text{Na}} > 30 \text{ mmol/L}$)
- Normal thyroid, adrenal and renal function


Causes of Syndrome of Inappropriate Anti-diuretic Hormone (SIADH):

- Pulmonary Disorders
  - Acute respiratory failure
  - Infections
  - Positive-pressure ventilation

- Tumors
  - Neoplastic
  - Pulmonary

- CNS Disorders
  - Acute psychosis
  - Hemorrhage
  - Inflammatory and demyelinating diseases
  - Mass lesions
  - Stroke
  - Trauma

- Miscellaneous
  - HIV infection
  - Idiopathic
  - Pain
  - Postoperative state
  - Prolonged exercise
  - Severe atrophy
  - Severe nausea

Current Treatment Strategies

<table>
<thead>
<tr>
<th>AGENT</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid restriction</td>
<td>- Slow to correct over days (1-2 mEq/L/day)</td>
</tr>
<tr>
<td></td>
<td>- Poorly tolerated due to thirst</td>
</tr>
<tr>
<td></td>
<td>- Should not be used with high AVP level and urine osmolality</td>
</tr>
<tr>
<td>Diuretics</td>
<td>- Potential for ototoxicity, volume depletion, and K⁺ and Mg⁺ depletion</td>
</tr>
<tr>
<td>Demeclocycline</td>
<td>- Not FDA approved for hyponatremia</td>
</tr>
<tr>
<td></td>
<td>- Slow to correct over days</td>
</tr>
<tr>
<td></td>
<td>- Nephrotoxic in cirrhosis and heart failure</td>
</tr>
<tr>
<td>Lithium</td>
<td>- Slow to correct</td>
</tr>
<tr>
<td></td>
<td>- Must monitor serum levels</td>
</tr>
<tr>
<td></td>
<td>- CNS side effects, cardiotoxic, GI disturbances</td>
</tr>
</tbody>
</table>
Urine Concentration Determines the Stringency of Water Restriction

72-year-old woman with hypotonic hyponatremia; obligate solute load = 600 mOsm/d

\[ U_{osm} = 300 \text{ mOsm/kg}; \text{ fluid restriction of 2 L/d required to maintain } [\text{Na}^+]; 1.5 \text{ L/d necessary to correct hyponatremia} \]

\[ U_{osm} = 600 \text{ mOsm/kg}; \text{ fluid restriction of 1 L/d required to maintain } [\text{Na}^+]; 0.5 \text{ L/d required to correct hyponatremia} \]

Current Treatment Strategies

<table>
<thead>
<tr>
<th>AGENT</th>
<th>LIMITATIONS</th>
</tr>
</thead>
</table>
| Isotonic saline | • Ineffective in dilutional hyponatremia  
• Should not be used in setting of edema  
• No safety data  
• Complex calculations |
| Hypertonic saline | • No consensus regarding appropriate infusion rates  
• Overcorrection can cause osmotic demyelination syndrome  
• Should not be used in setting of edema  
• No safety data  
• Complex calculations |

Hypertonic Saline Considerations

• Use equations to calculate rate/duration  
  — Medication safety issues?  
• 7.1 mEq/L in 24 hours  
• 10% rate of overcorrection  
  — Higher risk for overcorrection when \([\text{Na}^+] < 120 \text{ mEq/L}\)
Overcorrection Defined

- Increase in Na⁺
  - Within 24 hours
    - >10 – 12 mEq/L
  - Within 48 hours
    - >18 mEq/L

What do they do?

Diuresis:
increased excretion of urine by the kidney;
includes water and typically increased solute excretion as well

Aquaresis:
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney

Newest Option for Hyponatremia:
Vasopressin Antagonists
Mechanism of Vasopressin Antagonists

Vasopressin $\rightarrow$ V$_2$ Receptors

Non-peptide AVP receptor antagonists

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Conivaptan</th>
<th>Lixivaptan</th>
<th>Satavaptan</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>IV</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Urine volume</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Na$^+$ excretion/24 hrs</td>
<td>↔</td>
<td>↔ low dose</td>
<td>↑ high dose</td>
<td>↔ ↔</td>
</tr>
</tbody>
</table>

CONIVAPTAN

Conivaptan: Pivotal Phase III Trial

- R, MC, DB, PC
  - n = 84 patients
- 4 day continuous infusion
  - Placebo
  - Conivaptan 40mg/day
  - Conivaptan 80mg/day
- Primary endpoint
  - ∆ in serum sodium from baseline (AUC)
- Secondary endpoints
  - Time from 1st dose to sodium ≥ 4mEq/L, time sodium ≥ 4mEq/L from baseline, # patients with ≥ 6mEq/L increase in sodium or normal (≥ 135mEq/L).

Patient Population

- Inclusion criteria
  - Age > 18 years
  - Serum Na⁺ = 115 – 130mEq/L
  - Po2m < 290mOsm/kg
  - Fasting BG < 275mg/dl
  - Euvolemic or hypervolemic

- Exclusion criteria
  - Hypovolemic hyponatremia
  - Uncontrolled HTN, bradyarrhythmia or tachyarrhythmias
  - Medications interact with CYP3A4
  - Emergent treatment for hyponatremia

## RESULTS

<table>
<thead>
<tr>
<th>Endpoint Placebo</th>
<th>Con 40mg IV</th>
<th>Con 80mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Δ</strong> in baseline Na AUC, mean (SE), mEq/h/L</td>
<td>12.9 (61.2)</td>
<td>469.9 (56.8) †</td>
</tr>
<tr>
<td>Time 1st dose to Na &gt; 4mEq/L from BL, median hrs (95% CI)</td>
<td>NE</td>
<td>23.7 (95%CI 0.0, 24.0) †</td>
</tr>
<tr>
<td>Total time serum Na above baseline, mean (SE), h</td>
<td>14.2 (5.25)</td>
<td>53.2 (5.17) †</td>
</tr>
<tr>
<td>Change in Na from baseline to end of treatment, mean (SE), mEq/L</td>
<td>0.8 (0.80)</td>
<td>6.3 (0.74) †</td>
</tr>
<tr>
<td>Increase Na &gt; 5mEq/L or &gt; 135mEq/L, n (%)</td>
<td>6 (20.7%)</td>
<td>20 (69.0%) †</td>
</tr>
</tbody>
</table>

† p < 0.001, NE = not estimable

---

### Conivaptan: open label extension study

![Conivaptan hydrochloride injection. Prescribing information; February 2006.](image)

Can we verify that this isn’t published, would prefer to NOT reference the PI unless necessary

### Conivaptan Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=29)</th>
<th>Con 40 mg (n=29)</th>
<th>Con 80 mg (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlebitis</td>
<td>6.9%</td>
<td>24.1%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6.9%</td>
<td>13.8%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>0%</td>
<td>13.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Injection Site Inflammation</td>
<td>0%</td>
<td>6.9%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0%</td>
<td>10.3%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3.4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection-site Thrombosis</td>
<td>0%</td>
<td>10.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Overcorrection</td>
<td>0%</td>
<td>6.9%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Special Populations: Heart Failure

- Do not use to TREAT heart failure
  - No benefit
  - No worsening of heart failure
- Risk of adverse effects must be outweighed by anticipated benefits of increasing sodium

Special Populations: Neurology

2 retrospective case series, neuro ICU patients

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Dosing</th>
<th>Timing</th>
<th>6mEq/L Rise</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>22</td>
<td>Bolus + Infusion</td>
<td>24 hrs</td>
<td>86%</td>
<td>No excessive correction 5 pts with phlebitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24h post D/C = 47%</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>24</td>
<td>Bolus only</td>
<td>72 hrs</td>
<td>Single Bolus: 56%</td>
<td>1 pt with excessive correction No phlebitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Double Bolus: 52%</td>
<td></td>
</tr>
</tbody>
</table>

Conivaptan: Practical Considerations

- 20 mg IV over 30 minutes, then 20 mg continuous IV infusion over 24 hours
  - May increase to 40 mg daily if inadequate response
  - Administer x 1 to 3 days
  - Only compatible with 5% dextrose.
  - Limited data on IV drug-drug compatibility.
  - To minimize the risk of vascular irritation
    - Administer through large veins
    - Change infusion site every 24 hours
- Contraindication: Co-administration with potent CYP3A4 enzyme inhibitors
  - ketoconazole, itraconazole, indinivar

TOLVAPTAN

SALT – 1 and SALT – 2
Study of Ascending Levels of Tolvaptan in Hyponatremia

- Two MC, R, DB, PC trials
  - Tolvaptan 15 mg (increased to 30 – 60 mg)
  - Placebo
- Primary Endpoints:
  - $\Delta$ in AUC for the serum Na$^+$ concentration
    - Baseline to day 4
    - Baseline to day 30


SALT – 1 and 2 Patient Population

- Inclusion criteria
  - > 18 years of age
  - Sodium < 135
  - CHF
  - Cirrhosis
  - SIADH
- Exclusion criteria
  - Hypovolemic hyponatremia
  - Cardiac surgery, MI, SVT, angina, CVA, Pulmonary HTN
  - Hypotension, Uncontrolled diabetes mellitus
  - Scr > 3.5mg/dl
  - Child-Pugh > 10

SALT – 1 RESULTS

AUC for serum Na+(mmol/L)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo n = 103</th>
<th>Tolvaptan n = 103</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients: Day 4</td>
<td>0.25 ± 2.08</td>
<td>3.62 ± 2.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All Patients: Day 30</td>
<td>1.66 ± 3.59</td>
<td>6.22 ± 4.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mild (130 – 135 mmol/L): Day 4</td>
<td>-0.32 ± 2.27</td>
<td>2.52 ± 1.95</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mild (130 – 135 mmol/L): Day 30</td>
<td>0.68 ± 2.78</td>
<td>3.87 ± 3.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Marked (&lt; 130 mmol/L): Day 4</td>
<td>0.76 ± 1.77</td>
<td>4.56 ± 2.88</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Marked (&lt; 130 mmol/L): Day 30</td>
<td>2.54 ± 4.01</td>
<td>8.24 ± 3.84</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: Na+ concentration similar to placebo within 5 days of D/C

SALT – 2 Data not shown but similar


Special Populations: Heart Failure

EVEREST TRIALS: Short-term

• 2 identical short term trials
• R, DB, PC, MC
• Patients:
  — Hospitalized for HF, EF < 40%, HF symptoms
  — Not required to have HYponatremia
• Treatment
  — Tolvaptan 30 mg daily
  — Placebo
• Primary Endpoint
  — Global clinical status and body weight
    • Discharge or 7 days

Special Populations: Heart Failure

EVEREST TRIALS: Long-term Outcomes

• Extension of short term trials
• Minimum 60 day treatment (median = 9.9 mos)
  — Tolvaptan/Placebo
    • On top of standard HF therapy
• Primary Endpoint
  — All-cause mortality
    • Superiority/Non-inferiority
  — Composite: CV death or hospitalization for HF
    • Superiority
• Secondary Endpoint
  — Δ in dyspnea, body weight, edema
Special Populations: Heart Failure

EVEREST TRIALS: Results

The Endpoints

Short – term results
- Global clinical status and body weight
  - Improvement with tolvaptan

Long – term results
- All-cause mortality
  - No difference
- Composite: CV death or hospitalization for HF
  - No difference
- Δ in dyspnea, body weight, edema
  - Improvement with tolvaptan

Konstam MA, et al. JAMA 2007;297:1319-31

Tolvaptan: Practical Considerations

- Indicated for symptomatic hyponatremia
  - < 125mEq/L
  - Unresponsive to correction with fluid restriction
  - In-hospital initiation
- Administered by oral route once daily
  - 15 mg/30 mg/60 mg
- Contraindication: Co-administration with potent CYP3A4 enzyme inhibitors
  - ketoconazole, itraconazole, indinavir
- Patients should be encouraged to drink when thirsty
- Co-administration with hypertonic saline: NR

Tolvaptan [package insert] 2009

Tolvaptan Adverse Effects

SALT studies
- No osmotic demyelination
- Excessive Na⁺ correction = 1.8%

EVEREST
- Thirst
- Polyuria
- Pollakiuria
- Hypernatremia
**HYponatremia Treatment Options**

- **Level 3 - Severe Symptoms:** vomiting, seizures, obtundation, respiratory distress, coma
  - Hypertonic Saline
- **Level 2 - Moderate Symptoms:** nausea, confusion, disorientation, altered mental status
  - Vasopressin Antagonist or Hypertonic Saline
- **Level 1 - No or Minimal Symptoms:** headache, irritability, inability to concentrate, altered mood, depression
  - Fluid restriction
  - Consider vasopressin antagonist or hypertonic saline if...
  - "Unable to tolerate fluid restriction or failure of fluid restriction"
  - "Need for rapid correction of Na"**

**Vasopressin Antagonist Formulary Considerations**

- **Vasopressin antagonist vs. Hypertonic Saline?**
  - Unable to tolerate fluids
  - Degree of hyponatremia
- **Restrict to a specific service?**
  - Endocrine, nephrology, hepatology?
- **Tolvaptan and insurance status**
  - Reversible effect on sodium upon discontinuation

**Conclusions**

- **Considerations in Management**
  - Pathophysiology/Classification
  - Symptoms (Type, Severity, Duration, Onset)
  - Underlying disease states
- **Primary treatment options**
  - Fluid restriction, Hypertonic saline, Vasopressin receptor antagonists
- **Role of the pharmacist**
  - Global policies related to use
  - Agent selection
  - Monitoring
Questions/Discussion

Question 8

How confident are you in your ability to summarize the Hyponatremia Treatment Guidelines: 2007 Expert Panel Recommendations?

1. Not at all confident
2. Somewhat confident
3. Confident
4. Very Confident
5. Extremely Confident

Question 9

Of patients treated for hyponatremia, what percentage are initially treated as inpatients?

A. 10% - 25%
B. 26% - 43%
C. 44% - 54%
D. 55%–63%
Question 10

Compared with standard diuretics, vasopressin receptor antagonists act at a different site of the nephron to induce selective water diuresis without affecting sodium and potassium excretion.

A. True
B. False

Patient Case: Asymptomatic Hyponatremia

- 75-yr female, stable CHF and type 2 DM
- Fell while coming down the stairs in her house, now experiencing severe leg pain and pleuritic chest pain
- ER: Left hip fracture, multiple rib fractures, small pleural effusions bilaterally, no pneumothorax
- Admitted to ICU for monitoring, physical exam: patient is awake and oriented; blood pressure is 130/80; heart rate is 76 bpm; no focal neurological deficits; bibasilar rales; point tenderness over rib cage

Patient Case: Asymptomatic Hyponatremia

Labs:

Na = 128, K = 3.4, Cl = 104, HCO3 = 24
glucose = 185, BUN = 20, Cr = 1.3
Hct = 36

Posm = 275, Uosm = 350, UNa+ = 60
O2 sat = 90% room air
Question 11

According to the ADHERE risk stratification which of the following factors places this patient at risk for mortality?

A. Her age  
B. Her blood urea nitrogen (BUN)  
C. Her Serum Na+  
D. Her heart rate

Question 12

The hyponatremic brain is NOT a normal brain, but rather represents a state of _________ as a result of solute losses.

A. Allostasis  
B. Homeostasis  
C. Static serum osmolality  
D. Normonatremia

Question 13

SIADH is characterized by (1) the presence of hyponatremia, (2) low plasma osmolality without volume depletion or edema, (3) high urine osmolality >100 mOsm/kg, (4) urine [Na+] excretion >20 mEq/L, and (5) normal renal, adrenal, thyroid, and cardiac function.

A. True  
B. False
Question 14
Which of the following is not a neurological manifestations commonly seen in cases of acute symptomatic hyponatremia?

A. Stupor/Coma  
B. Convulsions  
C. Atopy  
D. Respiratory Arrest

Question 15
According to data from the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT 1 and 2) serum sodium concentrations ________ in the tolvaptan group when compared to the placebo group during the first 4 days and after the full 30 days of therapy.

A. Did not change  
B. Increased  
C. Decreased  
D. Were equal

Question 16
How do you anticipate that your attendance at this educational program will change your clinical practice?  (Please select all that apply)

1. Improve my ability to recommend/develop institutional protocols for hyponatremia management  
2. Improve my compliance with Hyponatremia Treatment Guidelines: 2007 Expert Panel Recommendations  
3. Improve my ability to risk-stratify patients with presumed hyponatremia  
4. Improve clinical outcomes in my patients  
5. I do not anticipate a change in my practice