HYONATREMIA: WATER DISORDER

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Samaritan Health Services

Ten Most Frequently Used Search Terms in UpToDate (2010-2011)

1. Hyponatremia
2. Hypercalcemia
3. Gout
4. Pancreatitis
5. Pneumonia
6. UTI
7. Cellulitis
8. Hypertension
9. Hyperkalemia
10. Sinusitis

Case:

A 28-year-old male patient with a past medical history only significant for remote seizure disorder presented to ED with several days of intermittent nausea, vomiting, headache, and mild weakness. The patient sustained mild head trauma while drinking a week prior to this presentation. Only medication he was on was ibuprofen 200 mg one to two tablets every 6 hours.

Physical examination revealed a well-developed well-nourished young male in no acute distress. Temperature 37.5, pulse 45, respiratory rate 14, blood pressure 133/73 mmHg and O2 saturation 98% on room air. Physical examination was normal without any neurological deficit. There were no clinical signs of dehydration or volume overload. The CT of the brain showed right basal frontal hemorrhagic contusion with minor acute blood product.
Blood work in the ED revealed serum sodium of 120 mEq/L. Serum osmolality was 247 mOsm/Kg. Urine osmolality was 697 mOsm/kg. Serum uric acid was 2.8 mg/dL. His creatinine and BUN were normal at 0.7 and 14. His thyroid function and morning cortisol levels were normal. The patient was given a liter of normal saline in the ED. He was placed on 1.5 L/day of fluid restriction and continued at NS of 50 cc per hour. Next day his sodium went down to 111 mEq/L. Urine osmolality was 739 mOsm/Kg H2O. Urine sodium was 188 mmol/L. He had generated about 400 cc of urine overnight. At the time of my evaluation, he complained of mild headache and nausea.

What is the Most Likely Etiology?

1. Cerebral salt wasting syndrome
2. SIADH
3. Hypovolemic hyponatremia due to intractable nausea and vomiting
4. None of above

What Is the Appropriate Initial Therapy?

- Normal saline
- 3% Hypertonic saline
- Fluid restriction with salt tablets
- Fluid restriction, salt tablets, and a loop diuretic
- Vasopressin receptor antagonist
- None of above
What Should be the Daily Fluid Restriction?

- Less than 1.5 L
- Less than 1.0 L
- Less than 700 cc
- No fluid restriction since he is clinically dehydrated

What Are the Predictors of Fluid Restriction Failure in SIADH?

- High urine osmolality (> 500 mOs/kg H2O)
- Sum of urine Na⁺ and K⁺ greater than serum sodium
- 24-hour urine output < 1,500 ml/day
- All of above

Objectives: Hyponatremia

- Physiology of osmoregulation
- Diagnostic approach
- Clinical manifestation
- Management
Water and Sodium Balance

- Too much water - hyponatremia
- Too little water - hypernatremia
- Too much sodium - edema
- Too little sodium – volume depletion

The plasma sodium concentration is regulated by water and ECF volume is regulated by sodium

Body Fluid Compartments

Total Body Water (60% body weight)

- Plasma (5% body weight)
- Intracellular (40% body weight)
- Extracellular (20% body weight, 1/3 of TBW)
- Intracellular Water

Composition of the Intracellular and Extracellular Fluids

<table>
<thead>
<tr>
<th>ECF</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>K⁺</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>HPO₄²⁻</td>
</tr>
<tr>
<td>Proteins</td>
<td>Mg²⁺</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>Cl⁻</td>
</tr>
<tr>
<td>K⁺</td>
<td>Na⁺</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>HCO₃⁻</td>
</tr>
<tr>
<td>HPO₄²⁻</td>
<td>SO₄²⁻</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>Cl⁻</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>Na⁺</td>
</tr>
</tbody>
</table>

Tk.

10/4/2013
Definitions:

- **Osmolality**: The total number of solute particles (osmoles) dissolved in solution that results in the osmotic pressure responsible for water movement across cell membrane.

\[ \text{Posm} = 2 \times \text{plasma } [\text{Na}^+] + \text{[Glucose]}/18 + \text{BUN}/2.8 \]

\[ \text{Posm} \approx 2 \times \text{plasma } [\text{Na}^+] \]

- **Plasma** [\text{Na}^+] = \frac{\text{Na}_e^+ + \text{K}_e^+}{\text{TBW}}

Osmoregulation vs Volume regulation

- The plasma osmolality is regulated by changes in *water intake* and *water excretion*, while sodium balance is regulated by changes in sodium excretion.

- Osmoregulation is mediated by *ADH* and volume regulation is mediated by *renin-angiotensin-aldosterone*.
### Osmoregulation vs Volume Regulation

<table>
<thead>
<tr>
<th>What is sensed</th>
<th>Osmoregulation</th>
<th>Volume regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense</td>
<td>Plasma osmolality, primarily plasma sodium</td>
<td>Effective tissue perfusion</td>
</tr>
</tbody>
</table>

#### Sensors

- Hypothalamic osmoreceptors
- Glomerular AA
- Carotid sinus
- Aortic arch
- Atria

#### Effectors

- ADH
- Thirst
- Renin-All-Aldo
- ENS
- ANP, BNP
- ADH
- Thirst

#### What is affected

- Water excretion
- Water intake
- Urine sodium
- Water intake

### Vasopressin (ADH) Secretion

![Vasopressin (ADH) Secretion Diagram](image)

### Normal Serum [Na] (135-145 mEq/L) Closely Guarded

Response to changes in serum osmolality

![Normal Serum Na Diagram](image)
Regulation of Serum Osmolality

- Decreased Na concentration (water excess)
- Decreased osmolality
- Decreased thirst
- ADH release is suppressed
- Increased water excretion by kidneys
- Serum Na concentration/osmolality return to normal

- Increased Na concentration (water deficit)
- Increased osmolality
- Increased thirst
- ADH release increases
- Decreased water excretion by kidneys

- Reduced plasma osmolality or increased effective arterial volume

Thirst

Increased fluid intake

Vasopressin

Antidiuresis

Reduced plasma osmolality or increased effective arterial volume
Osmoregulation: Summary

- Vasopressin (ADH) is a polypeptide synthesized in the supraoptic and paraventricular nuclei in the hypothalamus
- The absence or presence of vasopressin is the major physiologic determinant of urinary free water excretion or retention
- Vasopressin acts on the collecting ducts, the site at which water can be reabsorbed or excreted
- The major stimuli to Vasopressin secretion are hyperosmolality and reduction in effective circulatory volume
**HYPONATREMIA**

**Hyponatremia: Definition**

<table>
<thead>
<tr>
<th>Serum [Na⁺] mEq/L</th>
<th>Severe hyponatremia</th>
<th>Mild hyponatremia</th>
<th>Normonatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 125</td>
<td>125-134</td>
<td>135-144</td>
<td></td>
</tr>
</tbody>
</table>

**Incidence of Hyponatremia in Acute Hospital Care**

<table>
<thead>
<tr>
<th>Incidence of hyponatremia by severity</th>
<th>&lt; 116</th>
<th>&lt; 126</th>
<th>&lt; 136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present on admission</td>
<td>0.5%</td>
<td>2.6%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>0.7%</td>
<td>3.7%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Total</td>
<td>1.2%</td>
<td>6.2%</td>
<td>42.6%</td>
</tr>
</tbody>
</table>

*Hawkins RC, Clin Chim Acta, 2003; 337 169-172*
Hyponatremia: Acute vs Chronic

Classification by rate of declining serum sodium:

- Hyponatremia
  - Acute: Serum sodium falls rapidly over a period of <48 hours
  - Chronic: Serum sodium falls slowly over a period of ≥48 hours

Falls Are a Common Symptoms of Chronic "Asymptomatic" Hyponatremia

Patients admitted for falls:

- Hyponatremic patients: 21.3%
  - Mean serum Na+: 125 ± 4 mEq/L (n=170)
- Control patients: 5.3%
  - Mean serum Na+: 139 ± 6 mEq/L (n=234)

Hyponatremia: Initial Evaluation

- **H&P**
  - Medications: SSRI, thiazide diuretics
  - PMH: prior pituitary surgery, trauma, CHF, cirrhosis
  - ROS: Symptoms attributable to acute or chronic hyponatremia
  - Symptoms suggestive of cause, eg profuse diarrhea – hypovolemic hyponatremia

- **Exam:**
  - Hypovolemic? Orthostasis, JVP
  - Hypervolemic? JVP, edema, chest exam

Laboratory Assessment of Hyponatremia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osmolality</td>
<td>275-290 mOsm/kg H₂O</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>50-1200 mOsm/kg H₂O</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>&lt; 20 mEq, low effective arterial volume state</td>
</tr>
<tr>
<td></td>
<td>&gt; 20-40 mEq/L euvolemic patients without decreased effective arterial volume</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td></td>
</tr>
<tr>
<td>Adrenal and thyroid function</td>
<td></td>
</tr>
<tr>
<td>Serum uric acid, BUN</td>
<td></td>
</tr>
</tbody>
</table>
Drugs are a Common Cause of Hyponatremia

- Diuretics/Thiazide
- Antidepressants
- Antipsychotics
- Antiepileptics
- Anticancer drugs
- NSAIDs
- PPIs

Acute Severe Hyponatremia: Cerebral Edema
Brain Volume Adaptation to Chronic Hyponatremia

Hyponatremia

Classification of Hyponatremia

Dilutional hyponatremia
- Hypervolemic
  - Congestive heart failure
  - Cirrhosis
  - Nephrotic syndrome
- Euvolemic
  - SIADH
  - Hypothyroidism
  - Secondary adrenal insufficiency

Depletional hyponatremia

Hypovolemic
- Diarrhea
- Vomiting
- Burns
- Trauma
- Pancreatitis
- Diuretic excess
- Renal salt wasting
- Mineralocorticoid deficiency
SIADH

Table 1 Diagnostic criteria for SIADH (10).

<table>
<thead>
<tr>
<th>Diagnostic criteria for SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential</strong></td>
</tr>
<tr>
<td>• Plasma osmolality &lt;270 mosmol/kg H$_2$O</td>
</tr>
<tr>
<td>• Inappropriate urinary concentration (U$_{osm}$ &lt; 100 mosmol/kg H$_2$O)</td>
</tr>
<tr>
<td>• Patient is clinically euvoaemic</td>
</tr>
<tr>
<td>• Elevated urinary sodium (&gt; 40 mmol/l), with normal salt and water intake</td>
</tr>
<tr>
<td>• Exclude hypothyroidism and glucocorticoid deficiency</td>
</tr>
<tr>
<td><strong>Supplemental</strong></td>
</tr>
<tr>
<td>• Abnormal water load test, i.e. inability to excrete at least 90% of a 20 ml/kg water load in 4 h and/or failure to dilute urine to U$_{osm}$ &lt; 100 mosmol/kg H$_2$O</td>
</tr>
<tr>
<td>• Plasma AVP levels inappropriately elevated relative to plasma osmolality</td>
</tr>
</tbody>
</table>

Causes of SIADH

- Pulmonary disorders
- Acute myocardial infarction
- Medications: 
  - Thiazides
  - Diuretics
- G6S disorders: 
  - Acute psychosis
  - Hemorrhage
  - Inflammatory and infiltrating diseases
- Neoplasms: 
  - Solid tumors
  - Leukemia
  - Lymphomas
- Drugs: 
  - Thiazides
  - Diuretics
  - Thioridazine
  - Phenytoin
  - Phenobarbital
  - Allopurinol
  - Retinoids
- Miscellaneous: 
  - Hypercalcemia
  - Hypothyroidism
  - Yoga
  - Postoperative state
  - Prolonged exercise
  - Same study
  - Seven causes
Effect of Isotonic Saline in SIADH

Assume that:

Plasma sodium: 114 mEq/L
Urine osmolality: 616 mOsm/kg

In SIADH, water handling is abnormal but sodium handling is intact.

<table>
<thead>
<tr>
<th>NaCl</th>
<th>H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 308</td>
<td>1000</td>
</tr>
<tr>
<td>Out 500</td>
<td></td>
</tr>
<tr>
<td>Net + 500 ml of water</td>
<td></td>
</tr>
</tbody>
</table>

To raise the plasma sodium with fluid in SIADH, 2 x \((\text{Na} + \text{K})\), concentration in the fluid given must exceed the osmolality of the urine.

### SIADH v.s. Cerebral Salt Wasting

<table>
<thead>
<tr>
<th></th>
<th>SIADH</th>
<th>CSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Na</td>
<td>Ž</td>
<td>Ž</td>
</tr>
<tr>
<td>ECF volume</td>
<td>Normal</td>
<td>Ž</td>
</tr>
<tr>
<td>(U_{\text{Na}})</td>
<td>Ŷ</td>
<td>Ŷŷ</td>
</tr>
<tr>
<td>(U_{\text{OSM}})</td>
<td>Ŷ</td>
<td>Ŷŷ</td>
</tr>
<tr>
<td>Urine volume</td>
<td>N or Ž</td>
<td>Ŷŷ</td>
</tr>
<tr>
<td>Serum urate</td>
<td>Ž</td>
<td>N or Ž</td>
</tr>
<tr>
<td>Urine urate</td>
<td>Ŷ</td>
<td>N or Ŷ</td>
</tr>
</tbody>
</table>
Osmotic Demyelination Syndrome (ODS)

- Dysarthria, dysphagia, paraparesis or quadriplegia
- Symptoms are often irreversible or only partially reversible
- Severely affected patients may become "locked in"; they are awake, but are unable to move or communicate
- Clinical manifestations of ODS are typically delayed for two to six days after overly rapid elevation of the serum sodium concentration

Osmotic Demyelination Syndrome

Risk Factors for ODS

- Chronic hyponatremia
- Alcoholism
- Malnutrition
- Liver disease
- Burns
- Hypokalemia
- Serum sodium < 105 mEq/L
Treating Chronic Hyponatremia

To maximize patient safety, goals of therapy should be more modest

- 6-7 mEq/L per 24 hours
- 12-14 mEq/L per 48 hours
- 14-16 mEq/L per 72 hours

Hyponatremia: Treatment

Add to the numerator

\[
\text{Plasma Na}^+ = \frac{\text{Na}^+ + \text{K}^+}{\text{Total Body Water}}
\]

Subtract from the denominator

Hyponatremia: Treatment

Insufficient Correction

Too aggressive correction

Cerebral edema

[Na\(^+\)]

ODS
Hyponatremia: Treatment

Considerations:

- ECF volume status
- Acute vs. chronic
- Symptoms

Initial treatment of hyponatremia according to extracellular volume status

Hypervolemic
- Fluid restriction
- Sodium restriction
- Loop diuretics
- Treat underlying fluid-retention state (see text)

Hypovolemic
- Intravenous isotonic saline
- Discontinue diuretics
- Replace mineralocorticoids if deficient

Euvolemic
- Fluid restriction
- Loop diuretics plus salt tablets to replace urinary sodium losses
- Demeclocycline (Declomycin)
- Vasopressin receptor antagonists
- Oral uro (not available in United States)
- Enhance solute intake if poor nutrition
- Discontinue medications associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Treatment of underlying carcinoma if ADH-secreting tumor
- Treatment of underlying condition associated with SIADH
  (eg, antibiotics for pneumonia)
- Treatment of endocrinopathy (eg, hypothyroidism)

Indications for 3% NaCl

- Symptomatic hyponatremia (SZ, coma)
- Acute severe hyponatremia (<24h, < 120 mEq/L)
- SAH with hyponatremia worsening on 0.9% NaCl
FIGURE 2. Tolvaptan (SAMSCA).

TABLE 6
Vasopressin antagonists for treating hyponatremia

<table>
<thead>
<tr>
<th>Vasopressin receptor</th>
<th>Tolvaptan (SAMSCA)</th>
<th>Ertapenem (IM, 100)</th>
<th>Sigamapant (IV, 30)</th>
<th>Conavaptan (CAPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>6-8</td>
<td>7-10</td>
<td>14-17</td>
<td>3.1-7.8</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP 3A4)</td>
<td>Hepatic (CYP 3A4)</td>
<td>Hepatic (CYP 3A4 90%)</td>
<td>Hepatic (CYP 3A4)</td>
</tr>
<tr>
<td>Dose</td>
<td>15-60 mg once daily</td>
<td>50-100 mg twice daily</td>
<td>5-25 mg once daily</td>
<td>20 mg in 30 minutes, then 20-40 mg/day</td>
</tr>
</tbody>
</table>


Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatremia


Hyponatremia: Treatment Considerations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic saline infusion</td>
<td>Rapid response in symptomatic patients, Complex calculations, Not commonly used in edematous state</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>Inexpensive, Slow and limited response, Requires severe restriction</td>
</tr>
<tr>
<td>AVP receptor antagonists</td>
<td>Targets excessive AVP at V2 receptor, Aquarexis, Expensive, Not to be used in hypovolemic state and patients requiring rapid correction of hyponatremia</td>
</tr>
</tbody>
</table>

Diagnostic and Therapeutic Approach to Hyponatremia

Case:
The diagnosis of SIADH due to head trauma was made. The patient was placed on fluid restriction, less than 700 cc per day. The patient was started on furosemide 20 mg twice daily along with the salt tablets 3 times daily. His serum sodium gradually rose to 120 the next 48 hours. On hospital day 5, he was discharged with a serum sodium of 131. His hyponatremia was completely resolved 3 weeks after discharge from hospital.