Hyponatremia

Eric Siddall, MD
Patient 1

• A 20F presents to the ED with obtundation. A few hours earlier she was at a club where she used ecstasy. Vitals-180/80, HR 50, minimal response to sternal rub. Labs Na 107, creatinine 0.8, glucose 80, serum osm 225. Urine osm 150. Head CT shows cerebral edema with obliteration of the ventricular spaces.

• Is this hyponatremia life-threatening?

• How should the hyponatremia be managed?
Patient 2

• A 53M w etoh abuse w seizures, CKD Cr 1.7, history of hyponatremia presents w altered mental status. On exam he is confused, but is conversant.
• Vitals AF, 108/74, 86, 16, 96% RA.
• Labs Na 96, k 3.2, Cl <60, HCO3 20, BUN 42, Cr 1.7
• Is this hyponatremia life threatening?
• How should the hyponatremia be managed?
Tonicity vs osmolality in Hyponatremia

- **Hypotonic**-gain of water dilutes serum Na. Most clinical cases of hyponatremia. Risk of cerebral edema.
  - Hyposmolar-most common clinical hyponatremia (hypovolemia, siadh, HF, etc)
  - Isosmolar-high BUN, etoh ingestion
  - Hyperosmolar-very high BUN
- **Hypertonic, hyperosmolar**-hyperglycemia, mannitol, IVIg (w sucrose/maltose diluent). Hypertonic solutions in ECFV draw water out of cells into ECFV. Not associated with a risk of cerebral edema.
- **Pseudohyponatremia**-reduction in aqueous fraction of sample by lipids/proteins leads to reduced measured Na in total sample. Normal tonicity. No risk of cerebral edema.

Oster Arch Int Med 1999; 159:333
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Condition</th>
<th>Serum Sodium, mmol/L</th>
<th>Blood Glucose, mmol/L (mg/dL)</th>
<th>Serum Urea Nitrogen, mmol/L</th>
<th>Mannitol or Ethanol, mmol/L</th>
<th>Osmo, mmol/kg H₂O</th>
<th>Osmol, mmol/kg H₂O</th>
<th>Osmol Gap, mmol/kg H₂O</th>
<th>Effective Osmolality, mmol/kg H₂O†</th>
<th>Risk of Cerebral Edema‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>140</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>0</td>
<td>290</td>
<td>290</td>
<td>0</td>
<td>285 (Normal)†</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Hyponatremia (without abnormal amounts of other solutes)</td>
<td>120</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>0</td>
<td>250</td>
<td>250</td>
<td>0</td>
<td>245 (Low)†</td>
<td>Increased</td>
</tr>
<tr>
<td>3</td>
<td>Pseudohyponatremia (eg, from extreme hypertriglyceridemia)</td>
<td>120</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>0</td>
<td>250</td>
<td>290</td>
<td>40</td>
<td>285 (Normal)†</td>
<td>Unchanged</td>
</tr>
<tr>
<td>4</td>
<td>Hyponatremia caused by severe hyperglycemia</td>
<td>120</td>
<td>75 (1350)</td>
<td>5 (14)</td>
<td>0</td>
<td>320</td>
<td>320</td>
<td>0</td>
<td>315 (High)†</td>
<td>Variable§</td>
</tr>
<tr>
<td>5</td>
<td>Hyponatremia caused by retention of mannitol</td>
<td>120</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>75</td>
<td></td>
<td></td>
<td>250</td>
<td>325</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Hyponatremia together with high serum urea nitrogen†</td>
<td>120</td>
<td>5 (90)</td>
<td>45 (126)</td>
<td>0</td>
<td>290</td>
<td>290</td>
<td>0</td>
<td>245 (Low)†</td>
<td>Increased</td>
</tr>
<tr>
<td>7</td>
<td>Hyponatremia together with high blood ethanol level¶</td>
<td>120</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>40#</td>
<td>250</td>
<td>290</td>
<td>40</td>
<td>245 (Low)†</td>
<td>Increased</td>
</tr>
<tr>
<td>8</td>
<td>Hyponatremia</td>
<td>160</td>
<td>5 (90)</td>
<td>5 (14)</td>
<td>0</td>
<td>330</td>
<td>330</td>
<td>0</td>
<td>325 (High)†</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
# Pseudohyponatremia

<table>
<thead>
<tr>
<th></th>
<th>Lipid/protein</th>
<th>Aqueous phase</th>
<th>Lipid/protein</th>
<th>Aqueous phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured Na in sample</td>
<td>140</td>
<td>122</td>
<td>140</td>
<td>122</td>
</tr>
<tr>
<td>Aqueous phase</td>
<td>93%</td>
<td>80%</td>
<td>93%</td>
<td>80%</td>
</tr>
<tr>
<td>Lipid/protein fraction</td>
<td>7%</td>
<td>20%</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Actual Na in aqueous phase</td>
<td>152</td>
<td>152</td>
<td>152</td>
<td>152</td>
</tr>
</tbody>
</table>
The serum Na is determined by only 3 variables

\[ \text{Na} = \frac{\text{Na}_E + \text{K}_E}{\text{TBW}} \]
Determinants of the serum Na

- Water
- Na, K
- Insensible losses
- Fever
- Sweat
- Stool
- Urinary losses
- Water Na, K
Determinants of urinary Water Loss

GFR
Intravascular volume
Osmolar excretion
VASOPRESSIN
Mechanisms of Hypotonic Hyponatremia

**Normal**

**Primary Water Gain**
- SIADH
  - idiopathic
  - malignancy
  - increased ICP
  - meds-ssri
- *Primary Polydipsia
- *ESRD
- *Low Osmolar Intake
- Hypothyroid
- Addison’s Disease

*denotes **NOT** associated with elevated serum vasopressin levels

**Primary Loss of Na and H2O**
- Hypovolemia
- Diarrhea
- Vomiting
- Diuretics (thiazides)

**Gain of Na and H2O**
- Generally all with low blood pressure
- Heart Failure (w low cardiac output)
- Childs C Cirrhosis
- Nephrotic syndrome
Electrolyte Free Water Clearance = \( V \times \left( 1 - \frac{UNa + UK}{SNa} \right) \)

\[ EFWC = \left( \frac{\text{Osmolar excretion}}{\text{Urine osmolality}} \right) \times \left( 1 - \frac{UNa + UK}{SNa} \right) \]
Osmolar excretion (mosm) = \[ \frac{\text{Urine Osm (mosm/kg)}}{\text{Urine Volume (L)}} \]

Normal

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18L</td>
<td>900mosm</td>
<td>50mosm/kg</td>
</tr>
<tr>
<td></td>
<td>900mosm</td>
<td>50mosm/kg</td>
</tr>
</tbody>
</table>

CKD

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6L</td>
<td>100mosm</td>
<td>150mosm/kg</td>
</tr>
<tr>
<td></td>
<td>900mosm</td>
<td>150mosm/kg</td>
</tr>
</tbody>
</table>

Low osmolar intake

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L</td>
<td>100mosm</td>
<td>50mosm/kg</td>
</tr>
<tr>
<td></td>
<td>900mosm</td>
<td>50mosm/kg</td>
</tr>
</tbody>
</table>

AKI

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3L</td>
<td>900mosm</td>
<td>300mosm/kg</td>
</tr>
<tr>
<td></td>
<td>900mosm</td>
<td>300mosm/kg</td>
</tr>
</tbody>
</table>

siadh

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L</td>
<td>900mosm</td>
<td>450mosm/kg</td>
</tr>
<tr>
<td></td>
<td>300mosm</td>
<td>450mosm/kg</td>
</tr>
</tbody>
</table>

ICU + AKI

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Urine Osm (mosm)</th>
<th>Osmotic Pressure (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>300mosm</td>
<td>300mosm/kg</td>
</tr>
<tr>
<td></td>
<td>300mosm</td>
<td>300mosm/kg</td>
</tr>
</tbody>
</table>

Assuming still make urine
Dependence of Free Water Clearance on Minimum Urine Osmolality and Dietary Osmolar Intake

At low solute (osmolar) intakes, water excretion is limited.

Uosm depends on vasopressin.
Necessary factors to excrete a maximally dilute urine

• Adequate distal delivery of water (adequate ECFV, adequate GFR)

• Functioning DCT (absence of thiazides)

• Absence of vasopressin
Vasopressin

- Released from posterior pituitary
- T½ of 15-20 minutes
- Primary stimulus for release is increased serum osmolality
- Secondary (and higher threshold, higher potency) stimulus is hypotension
- Action in kidney (V2R)-insertion of aquaporin channels in the apical collecting duct membrane making it permeable to water
Vasopressin

- Increases urea reabsorption in the collecting duct increasing medullary osmolality which increases free water reabsorptive capacity

- In a study of inpatients with hyponatremia, 97% had detectable vasopressin when assayed

Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.

Hemodynamic

Hypovolemic stimulus to ADH release

Relationship of plasma antidiuretic hormone (ADH) concentrations to isosmotic changes in blood volume in the rat. Much higher ADH levels can occur with hypovolemia than with hyperosmolality, although a relatively large fall in blood volume is required before this response is initiated.  

Factors Stimulating vasopressin Secretion

• Stimuli
  – Hyperosmolality
  – **Hypotension** (baroreceptor)
  – Stress-pain
  – Nausea
  – Pregnancy
  – Drugs (cytoxan, carbamazepine, SSRI)

• Inhibitors
  – Hypoosmolality
  – Hypervolemia
  – EtOH
Vasopressin release is part of the integrated response to hypotension

↓BP

1. Stimulation of sympathetic nervous system
   1. Systemic vasoconstriction
   2. ↑HR, ↑contractility
   3. Activation of renal sympathetic nerves
      afferent/efferent vasoconstriction → ↓RBF
      ↑prox tubular Na reabsorption (α1 receptors)
      renin secretion

2. ↑Vasopressin release

↓Delivery of fluid to the diluting segments of the nephron

↓Free water excretion

Activation of carotid/aortic baroreceptors

Activation of renal afferent baroreceptors

↑renin release

↑AT2 release

↓RBF, maintain GFR, ↑filtration fraction

↑prox tubular Na reabsorption

↑aldosterone release

↓distal tubular flow

↓macula densa Cl

↑renin
Acute Hyponatremia

ECF Brain
Na 140 Osm 290

ECF Brain
Na 120 Osm 230

ECF Brain
Na 120 Osm 230

Extracellular Na, Cl
Minutes -6hrs

Intracellular K
6hrs-48hrs

Organic osmolytes
24hrs-48 hrs

Adaptation-70% electrolyte, 30% osmolyte

CHRONIC
Rapid correction of chronic Hyponatremia

ECF | Brain
---|---
Na 110 | Osm 220
Na 130 | Osm 270

Slow correction of chronic hyponatremia

ECF | Brain
---|---
Na 110 | Osm 230
Na 115 | Osm 240

Na, Cl 24 hours
K 24 hrs
Osmolytes 7 days
Chronic Hyponatremia Implies Significant Osmolyte Losses

Acute Hyponatremia

Loss of Na, Cl, K

Acute Hyponatremia

Loss of osmolytes

Chronic Hyponatremia

Osmolyte losses facilitate return of the brain Volume to normal despite a very low osmolality

The cost of adaptation w osmolyte losses Is the risk for ODS if hyponatremia is corrected rapidly
Adaptation to acute hyponatremia is oxygen dependent

Subjects - Rabbits
Hyponatremia - 2hrs @118 meq/L
Hypoxia - 40min @pO2 23mmHg

Ayus Kid Intern 2006; 69:1319
Mechanisms of Hyponatremia

Decreases in electrolyte free water excretion
*CKD 5/ESRD
*low osmolar excretion
*elevated serum vasopressin
  *hypovolemia
  *hypotension w low output HF, advanced cirrhosis, nephrotic syndrome
*SIADH physiology
  *increased intracranial pressure
  *diffuse pulmonary disease
  *cancer
  *meds-SSRI, cyclophosphamide, carbamazepine/oxcarbazepine
  *use of desmopressin for DI, enuresis, von Willebrand’s disease

Increased Free water intake (relative to excretory capacity)
  *polydipsia

Hypoadrenalism
  *Primary-combination of hypovolemia (hypoaldo) and hypocortisolism
  *secondary-lack of cortisol (removes tonic inhibition of vasopressin release)
    *ipilimumab-autoimmune hypophysitis

Hypothyroid-unclear mechanism, it must be very severe. SIADH picture.
Causes of Acute Hyponatremia
a minority of clinical hypoantremia

- **Post-surgical** (administration of hypotonic IVF to a patient w elevated vasopressin levels)
- **Exercise associated**
- **Ecstasy use** (extreme thirst + vasopressin release)
- **Psychogenic polydipsia** (often they also have increased vasopressin or reduced GFR in addition)
Chronic Hyponatremia
The majority of clinical hyponatremia

- Often multifactorial (particularly w severe hyponatremia)
- Hypovolemia
- ECFV expansion-HF, cirrhosis (both w hypotension)
- Euvolemia-SIADH (cancer, SAH, diffuse pulm disease, meds)
- Thiazides
- Low osmolar intake
# Hyponatremia-Clinical Presentation

<table>
<thead>
<tr>
<th>Acute</th>
<th>Acute on Chronic</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stupor/obtundation/coma</td>
<td>Impaired memory, confusion, delirium, lethargy, headache</td>
<td>Obtundation/coma has been seen in severe cases (Na &lt;105)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Nausea, vomiting</td>
<td>Lack of hypoxia</td>
</tr>
<tr>
<td>hypoxia</td>
<td>Gait disturbances, weakness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures can be present (usually with very low Na ~105 or less)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obtundation/coma has been seen in severe cases (Na &lt;105)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of hypoxia</td>
<td></td>
</tr>
</tbody>
</table>
Menstruating women are at higher risk for cerebral edema and associated brain injury from hyponatremia as compared to men or post-

Case control and cohort study of adults w Post op hyponatremia w and w/o Hyponatremic encephalopathy

23 women had autopsy- All had cerebral edema
Classification of Hyponatremia - Acute vs Chronic

- Onset of hyponatremia is seldom known, unless it occurs in the hospital.
- Inability to accurately classify hyponatremia based on time of onset leads to confusion regarding treatment strategies.
- Onset of mental status changes (if present) may not correlate w onset of hyponatremia.
- Use of new med (hctz) may not correlate w onset of hyponatremia.
Acute vs Chronic hyponatremia may be misclassified even when onset is known

• Prospective study of chronic hyponatremia in 53 hospitalized patients
• All pts had Na <130mmol/L that developed over at least 48 hrs and decreased by ≤ 0.5mmol/L/hr
• 6/11 that had neuroimaging performed had cerebral edema
• 3/5 with autopsies had cerebral edema
• Thus, even using accepted criteria, patients may have clinical evidence of cerebral edema despite being classified as chronic hyponatremia.

Ayus JAMA 1999; 281:2299
Neurologic symptoms

• Hyponatremia can lead to cerebral edema
• The presence of absence of cerebral edema determines the need for rapid or slow therapy
• The presence of severe neurologic symptoms denotes significant cerebral edema, whereas mild or no neurologic symptoms indicates the lack of clinically significant cerebral edema
• Thus, treatment should be based on the presence of absence of severe neurologic symptoms
• Severe neurologic symptoms = stupor/obtundation/coma, seizures, hypoxia
Acute Hyponatremia vs Chronic Hyponatremia

Hyponatremia with severe neurologic symptoms
Vs
Hyponatremia without severe neurologic symptoms
How to Manage Hyponatremia with Severe Neuro Symptoms?
Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury*

Claire Battison, BA Hons; Peter J. D. Andrews, MD; Catriona Graham, MSc; Thomas Petty

<table>
<thead>
<tr>
<th></th>
<th>Before Median</th>
<th>After Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP mm Hg</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Blood Na mmol/L</td>
<td>149</td>
<td>153</td>
</tr>
</tbody>
</table>
Figure Changes in physiologic variables before and after administration of 23.4% saline bolus
(A) Glasgow Coma Scale, (B) serum sodium concentration, (C) intracranial pressure, (D) cerebral perfusion pressure, (E) mean arterial pressure, (F) heart rate, and...
Hyponatremia w/ severe neuro sx - management

- Goal to increase Na by up to 6 meq/L in 1-2 hours
- **The only acceptable management strategy is hypertonic saline**
- Give 100cc 3% saline as a bolus q15min for a max of 3
- Can give 1amp (50meq) NaHCO3 IV in lieu of 100cc 3% saline
- If hypoxic, consider emergent intubation
- After the 1st 1-2 hours
  - Acute mechanism present - may not need to limit further increase in Na
  - Not due to an acute mechanism - maintain Na increase at 6 for the next 23hrs
True Acute Hyponatremia Can Be Correctedly Rapidly Without Fear of Post-Corrective Neurologic Sequelae

Serum Na in 27 episodes of Symptomatic Hyponatremia (seizures) in patients with psychogenic polydipsia

<table>
<thead>
<tr>
<th></th>
<th>Serum Na (mmol/L) Mean +/- SD</th>
<th>Serum Na (mmol/L) Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of hyponatremia</td>
<td>110.0 +/- 1.2</td>
<td>98-120</td>
</tr>
<tr>
<td>12 hours after treatment</td>
<td>125.9 +/- 1.0</td>
<td>116-140</td>
</tr>
<tr>
<td>24 hours after treatment</td>
<td>132.4 +/- 0.9</td>
<td>123-140</td>
</tr>
<tr>
<td>48 hours after treatment</td>
<td>136.3 +/- 0.9</td>
<td>126-143</td>
</tr>
<tr>
<td>Absolute change 12 hours After treatment</td>
<td>15.1 +/- 1.2</td>
<td>5-30</td>
</tr>
<tr>
<td>Absolute change 24 hours after treatment</td>
<td>21.6 +/- 1.4</td>
<td>9-34</td>
</tr>
<tr>
<td>Absolute change 48 hours after treatment</td>
<td>25.9 +/- 1.4</td>
<td>15-35</td>
</tr>
</tbody>
</table>

No episodes of post-corrective Neurologic sequelae

Patient 1

• A 20F presents to the ED with obtundation. A few hours earlier she was at a club where she used ecstasy. Vitals-180/80, HR 50, minimal response to sternal rub. Labs Na 107, creatinine 0.8, glucose 80, serum osm 225. Urine osm 150. Head CT shows cerebral edema with obliteration of the ventricular spaces.

• Is this hyponatremia life-threatening?

• How should the hyponatremia be managed?
Management

• 300cc 3% saline over 30min (would give faster if there was a central line)
• Would continue a 3% infusion to get the Na up by at least 12meq/L given severity of edema
• Ensure no free water being given in drips
• If UOP increases by 200cc/hr or more I would hold 3%
Part II
Hyponatremia without severe neuro symptoms
Osmotic Demyelination Syndrome (ODS)  
Formerly CPM/EPM

- Is a neurologic syndrome consequential to the rapid correction of chronic hyponatremia
- Probably an uncommon event
  - Of 254 patients with a Na ≤120, 37 over-corrected (≥12meq/L/day), 4/37 developed ODS. (Vu Hosp Practice 2009; 37: 128)
  - Of 606 patients with a Na ≤120 who corrected by >8meq/L/day, 7 developed ODS (1.1%). (George CJASN 2018; 13:984)
- Described in patients with hyponatremia whose Na increases by 10meq/L or less in 24hrs
- Usually occurs in patients with a Na ≤115
- Described in patients with Na ≥120 who have had a liver transplant or who chronically use dDAVP
- Has been described without hyponatremia in those with severe K deficiency that are corrected rapidly
- Azotemia appears to be protective against the development of ODS
ODS in Sweden

- Incidence 0.271 cases per 1 million patient years from 1997-2001
- Incidence of 0.945 cases per 1 million patient years from 2007-2011
- 69.9% alcoholics

<table>
<thead>
<tr>
<th>Sodium at admission (n = 83)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia (&lt;135 mmol/L)</td>
<td>72 (86.7%)</td>
</tr>
<tr>
<td>Sodium ≤ 110 mmol/L among hyponatremic patients (n = 72)</td>
<td>54 (75.0%)</td>
</tr>
<tr>
<td>Sodium &gt;110 mmol/L among hyponatremic patients (n = 72)</td>
<td>18 (25.0%)</td>
</tr>
<tr>
<td>Median sodium among hyponatremic patients (n = 72)</td>
<td>104 mmol/L (IQR 99.5-110.5)</td>
</tr>
<tr>
<td>Hyponatremia (&gt;146 mmol/L)</td>
<td>3 (3.6%)</td>
</tr>
<tr>
<td>Normonatremia (135-146 mmol/L)</td>
<td>4 (4.8%)</td>
</tr>
</tbody>
</table>

Aegisdottir, H. Acta Neurol Scandinav 2019; 140:342
ODS Risk Factors

- Na <115
- Alcoholism
- Cirrhosis
- Malnutrition
- Hypokalemia
- Thiazide diuretics
- Hypovolemia

George CJASN 2018; 13:984
ODS-clinical presentation

- Often initial improvement in mental status followed by neurologic deterioration 2-5 days after correction of hyponatremia
- Neuro symptoms
  - Confusion, altered mental status
  - Pseudobulbar palsy
  - Quadriparesis
  - Ventilatory failure
  - Seizures
  - Parkinsonism
- Outcome-irrespective of the severity of symptoms, up to 50% will have a good neuro outcome (no or minor disability), while the other half will have variably severe disability
ODS-Diagnosis

• Generally based on clinical impression
• MRI generally positive ~2 weeks after onset of symptoms
• Increased T2 signal intensity is the typical finding
• Some case reports suggest DWI imaging can be positive before T2, while others have not found this
ODS management

- Few options—prevention is critical
- Relowering of the Na prior to the onset of neuro symptoms prevents ODS in rats [Soupart Kid Int 1994; 45:193]
- Relowering of the Na after the onset of neuro symptoms reduces the severity of neuro sx and brain histology in rats [Soupart J Neuropathol Exp Neurol 1996; 55:594]
- Three case reports in humans have demonstrated that relowering of the Na after the onset of ODS symptoms reversed the symptoms [Soupart Clin Nephrol 1999; 51:383, Oya Neurology 2001; 57:1931, Croxson N Z Med J 2005; 118:U1661]
- In rats steroids, statins, minocycline reduced the severity of ODS lesions in those rapidly corrected
Hyponatremia without severe Neuro Symptoms-Goals

• Risk factors for ODS
  – Goal increase in Na of 4-6meq/L/24hrs
• No risk factors for ODS
  – Goal increase in Na 8-10meq/L/24hrs
• Since the patients do not have severe symptoms there is no benefit to raising the Na quickly. On the other hand, there is harm to raising it too quickly. Since an increase in Na of 6 will reduce cerebral edema, this is a reasonable amount to increase the serum Na in those without severe neuro sx.
Hyponatremia Work-up

- History-new meds, vomiting, diarrhea, history of HF, cirrhosis, psychotic disease, fluid intake
- Meds-thiazides, SSRI, carbamazepine
- Uosm (time dependent effects post IVF)
- Urine Na (confounders), FENa
- BUN/Cr, uric acid
- Cortisol, TSH
- Response to volume expansion
Pathophysiologic Based Management

$$Na = \frac{Na_E + K_E}{TBW}$$

 Electrolyte Free Water Clearance $=$ $V \times \left(1 - \frac{UNa + UK}{SNa}\right)$

$$EFWC = \left(\frac{\text{Osmolar excretion}}{\text{Urine osmolality}}\right) \times \left(1 - \frac{UNa + UK}{SNa}\right)$$
EFWC = \left( \frac{\text{Osmolar excretion}}{\text{Urine osmolality}} \right)

\text{\uparrow\text{Osmolar intake}} \rightarrow \text{\uparrow\text{osmolar excretion}}

*NaCl (NS, 3%, NaCl tabs)
*urea

\text{\downarrow\text{urine osmolality}}

Remove stimulus for vasopressin secretion
*volume repletion
*treat pain/nausea
*stop drugs that cause vasopressin release-SSRI, carbamazepine, oxcarbazepine, cytoxan
*treat low output HF
*vasoconstrictors/albmin for HRS
*cortisol/TSH replacement

Reduce urinary concentrating mechanism
*loop diuretics (little benefit if Uosm <300)

Antagonize Vasopressin-vaptans
Free Water Restriction

- Efficacy varies depending on urinary electrolyte content
- If urine Na + K/serum Na is <0.5, there is significant free water excretion. Fluid restriction to 1L will lead to an increase in Na.
- If urine Na + K/serum Na is >0.5 there is little free water excretion and restriction to 500cc would be necessary
- If urine Na +K/serum Na is >1, there is negative electrolyte free water excretion. The Na will decline even if the patient is npo.
The hypovolemic patient

• Option 1-give normal saline at high rates and cross your fingers
• Option 2-given normal saline at high rates and give desmopressin as needed
• Option 3-give normal saline at an extremely slow rate (ie 35cc/hr x 500cc and re-eval)
• Option 4-give small volume of 3% saline, then let them take po on their own
Loop diuretics inhibit the urinary concentrating mechanism

↓medullary osm =
↓gradient for water reabsorption =
↑free water excretion
Saline + loop diuretic for SIADH

\[
\begin{align*}
\text{Saline} & \quad \uparrow \text{Na}_E \\
 & \quad \text{-------------} \quad = \quad \uparrow \text{Na} \\
 & \quad \downarrow \text{TBW} \\
\downarrow \text{UOSM} \\
\text{Loop diuretic}
\end{align*}
\]
Effect of Urea on Na, Uvol, Una in a patient w SIADH

Oral Urea
- increases urine Vol
- decreases urine Na excretion
- increases the serum Na
Treatment of severe hyponatremia with urea and isotonic saline

Decaux G. Critical Care. 2010; 14:R184
Urea reduces urine Na excretion and increases free water excretion

Urea loading
-↑ urea reabsorption
In CD which ↑medullary [urea]
-↑medullary [urea] increases
Passive thin descending H₂O reabsorption
-↑thin ascending NaCl reabsorption
-higher tubular [urea] will reduce gradient
For water reabsorption
(and thus water excretion) from
The collecting duct
Vaptans inhibit vasopressin, thus blocking aquaporin channel insertion.
Vaptans inhibit vasopressin, thus blocking aquaporin channel insertion.
Rapid Correction

Rapid correction occurs when there is a rapid ↓ in TBW
Rapid correction is especially likely when Na is added to the body while TBW is ↓
Rapid decreases in the TBW usually occur when-
--there is a suppressible cause of vasopressin present
  * IVF for hypovolemia
  * off-set of medication (SSRI, thiazide)
  * simultaneous administration of K for hypokalemia (particularly w thiazides)
  * steroid administration to patient w addison’s
--there is presentation of a large number of osmoles to the distal nephron in a patient
  with low baseline osmolar excretion
  * tea and toast diet
  * beer potomania
--use of vaptans

Sterns Semin Nephrol 2009: 29:282
Case

- 70F w HTN, depression presents w 5 days of unsteady gait and mild confusion. She had a gi illness w diarrhea 10 days ago that lasted for 4 days. Has been drinking to ‘keep her fluids up.’ Meds include SSRI, hctz.
- ED-110/60, hr 106, awake, confused, responds to questions. Flat neck veins, clear lungs, no LE edema.
- Labs-Na 108, BUN 30, Cr 1.6 (baseline Cr 1.3)
- ED gives 1L saline over 2 hours
- Labs done 8 hours later show Na 122. Her urine specimen is clear w SG 1.003, urine Na 20, osm 80
- What happened?
Wt 70 kg
TBW 35L

Amount that 1L of a fluid will increase serum Na-

\[
\text{Infusate [Na] – serum [Na]} \quad 154-108 \\
\text{-----------------------------------} \\
\text{TBW +1} \quad 36 \\
\]

\[
\text{Na}_E + K_E \\
\text{Na=} \quad \frac{3780 \text{meq Na}}{35 \text{L}} = 108 \text{meq/L} \\
\text{TBW} \\
\]

\[
\frac{3780 + 154}{32.5 \text{L}} = 121 \text{meq/L} \\
\]
Case

- 70F w HTN, CKD baseline Cr 2.4 EGFR 25, depression presents w 5 days of unsteady gait and mild confusion. She had a gi illness w diarrhea 10 days ago that lasted for 4 days. Has been drinking to ‘keep her fluids up.’ Meds include SSRI, hctz.
- ED-110/60, hr 106, awake, confused, responds to questions. Flat neck veins, clear lungs, no LE edema.
- Labs-Na 108, BUN 30, Cr 3.1 (baseline Cr 2.4)
- ED gives 1L saline over 2 hours
- Labs done 8 hours later show Na 113. Her urine specimen shows SG 1.015, urine Na 50, uosm 180
- Why didn’t she correct rapidly?
Case

- 65M w dm2, HTN presented to the hospital 4 days ago with SAH. His aneurysm is coiled and he receives hypervolemic therapy with high volumes of saline.
- BP 130/80, hr 80
- Admission Na 136, current Na is 126.
- In the last 48 hours he has received 5L saline
- He is intubated (npo), and he has received 500cc free water in drips per day
- Urine Na 120, Uosm 600
- Tsh/cortisol normal
- Why is he hyponatremic?
**Desalination**

<table>
<thead>
<tr>
<th></th>
<th>Meq</th>
<th>Osm/kg</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uosm 600mosm/kg</td>
<td>300</td>
<td>---------</td>
<td>The 300meq will be excreted in 500cc of Urine at an osm of 600mosm/kg, thus</td>
</tr>
<tr>
<td>Saline 300meq/L</td>
<td>-------</td>
<td>600</td>
<td>500cc of free water will be generated For each liter of saline administered</td>
</tr>
<tr>
<td>Uosm 600mosm/kg</td>
<td>1000</td>
<td>---------</td>
<td>The 1000mosm will be excreted in 1.7L Of urine at an osm of 600mosm/kg, thus</td>
</tr>
<tr>
<td>3% saline 1000 meq/L</td>
<td>-------</td>
<td>600</td>
<td>Leading to the loss of 700cc of urine</td>
</tr>
</tbody>
</table>

Desalination represents the ‘risk’ of giving a volume challenge to someone with Hyponatremia in which the mechanism is unclear.

Giving a solution that exceeds the osm of the urine will prevent desalination in someone With siadh.
Consider the same patient-

torsemide 5mg po
lasix 10mg IV
Uosm 600mosm/kg----------------->Uosm 300mosm/kg

Now the addition of salt tabs, or 2% saline will facilitate an increase in the serum Na. At the least, administration of saline will no longer lead to progressive hyponatremia.

Another option would be tolvaptan along with saline (lower UOSM w tolvaptan so That the patient will tolerate saline without desalination)

Even mild hyponatremia in the neurosurgical patient is dangerous because they Often already have cerebral edema owing to a CVA, SAH, or ICH. Thus goal is to always Keep Na in the normal range or sometimes >140.
Case

- 52M w dm2, HTN who presented with nausea, vomiting, confusion. Due to feeling unwell, he has drank 12L bottled water per day x at least 2 days about 4 days ago.
- Exam-AF 161/77, 95, 18. He is conversant but confused and delirious.
- BMP 103 4.0 68 19 7 0.7 gluc 211
- ED gives some amount of saline→4hrs later Na 107
- Is this life threatening?
- How should he be managed?
Management-desmopressin

- Desmopressin 1mcg IV SC q8
- Later desmopressin 3mcg IV SC q8 with periodic free water administration
- Be very cautious giving desmopressin to a person who has psychogenic polydipsia or a psychiatric disorder
Use of DDAVP to slow or reverse rapid correction of hyponatremia in the ICU

Rafat CJASN 2014; 9: 229
Case

• 20F w bipolar presents w headaches, nausea. Na 121. Discharged from the ED after tylenol, reglan.

• Represents the following day w similar symptoms. Na 120.

• Receives 2L saline. Six hours later Na is 136.

• What do you do?
Reversing Rapid Correction

Give free water IV

Even if you give our patient 1L of D5W over 1hr, she will rapidly excrete it

Need to give DDAVP so she can retain the water

Plan
* give 2mcg DDAVP IV STAT
* give 1L D5W IV over 2 hours
* repeat BMP 3 hrs
* give more or less free water to get Na down to goal level ~128
* will need standing ddavp q8 to maintain free water retention
* free water restrict patient and only give water IV (to prevent large decreases in Na)

Since the Na increased quickly, it can be decreased quickly without fear of cerebral edema
Problems with using ddavp in hyponatremia to prevent or reverse rapid correction

• DDAVP induces an siadh state which can result in progressive hyponatremia due to ongoing free water intake
• DDAVP introduces the problem of desalination (any isotonic fluid will decrease serum Na if uosm is significantly >300)
• In my experience its effect can persist for ~24 hours
• In the setting of ddavp use, one must give high dose salt tabs or hypertonic saline to raise the serum Na
• When ddavp wears off, the water diuresis you were trying to prevent will occur; so requires repeat dosing
Patient 2

• A 53M w etoh abuse w seizures, CKD Cr 1.7, history of hyponatremia presents w altered mental status. On exam he is confused, but **is conversant**.

• Vitals AF, 108/74, 86, 16, 96% RA.

• Labs **Na 96**, k 3.2, Cl <60, HCO3 20, BUN 42, Cr 1.7

• Is this hyponatremia life threatening?

• How should the hyponatremia be managed?
Management-
3% saline and desmopressin

- Desmopressin 2mcg IV q8, 3% saline at 30cc/hr
- 1st 24hrs Na 96→102 △6
- 2nd 24hrs Na 102→114 △12
- 1st 48hrs △18
Coadministration of hypertonic saline and dDAVP

Controlled Correction

• Giving DDAVP stabilizes the Uosm and therefore the TBW
• Giving hypertonic saline (2% or 3% depending on uosm) allows one to increase the Na at a steady rate by adding Na
• Drawbacks-causes volume expansion, 3% can only be given in SDU or ICU

\[
Na = \frac{Na_E + K_E}{TBW}
\]
Use of DDAVP and D5W to reverse rapid correction of hyponatremia

Correction of hyponatremia w DDAVP and 3% saline in a controlled fashion

Perianayagam CJASN 2008 3; 331

Sterns Am J Kid Dis 2010; 56: 774
Case

• 70M alcoholic presents w confusion. He can speak, though is delirious, and falls asleep during the interview.
• BP 100/70, HR 100
• Na 102, BUN 24, Cr 0.8
• Wt 70kg
• How should this case be managed?
70kg male
TBW 42L
Na 102
Goal Na in 24 hrs 106-108

Na infusate-Na serum
------------------------------- =amount 1L of a fluid will increase the serum Na
TBW + 1

514meq/L-102meq/L
------------------- = 9.6meq/L
42L +1

Goal of 6meq/L
------------------- =625cc of 3% saline in 24hrs→26cc/hr
9.6meq/L

Formula only valid when Vasopressin on board
Plan-place foley
begin 26cc/hr 3% saline
after 2hrs give ddavp 2mcg IV, then 1mcg q12
check bmp q4hrs
for urine vol >200cc/hr increase ddavp to 2mcg q12
fluid restrict to 500cc/day
if Na not increasing enough, increase rate of 3%
if Uosm >300, reduce dose of ddavp

24hrs later...
-Na 104
-urine volume 900cc
-uosm 450
-BUN/Cr 20, 0.7

Why is Na not higher?
-he is drinking (or receiving IV) free water
-he is not losing any water in his urine

What to do
-reduce ddavp to 0.5mcg q12 (goal uosm ~300)
-increase 3% to 42cc/hr
Tolvaptan

- Only oral vasopressin antagonist approved in US
- Peak effect is hr 4-8
- Concerns about rapid correction (tolvaptan induces transient diabetes insipidus)
- Replace an increase in urine volume >200cc/hr w D5W
- Black box warning in cirrhotics
- Not labeled for use >1mo (though it is safe)
- Must be started in the hospital
- Metabolized through CYP3A4-drug interactions can increase/decrease tolvaptan effect
- Tolvaptan induces thirst which can limit its efficacy
Baseline Na, BUN, eGFR predict rapid correction of hyponatremia from SIADH with tolvaptan

Morris AJKD 2018; 71(6):772
Rapid Correction of hyponatremia with tolvaptan is more likely in SIADH vs HF

Morris AJKD 2018; 71(6): 772
Dosing

• UOSM <300 start 7.5mg
• UOSM >300 start 15mg, increasing by 15mg each day if no effect
• If UOSM is >500, 30 or 45mg will be necessary
• Don’t give lasix and tolvaptan together on the first day tolvaptan is started (can have massive urine volume)
Desmopressin associated hyponatremia

- Can be acute (severe neuro sx) or chronic (mild neuro sx)
- In a review of 13 cases of ddavp associated hyponatremia that led to neuro injury and were evaluated for QA, all were managed by holding desmopressin and giving IVF (usually 3% saline)
- After stopping ddavp, all patients had an increase in urine volume of >200cc/hr
- The mean 48hr increase in Na was 37.1meq +/- 8.4
- Outcomes-death 23%, severe brain damage 69%, moderate brain damage 8%
- 11 patients w neuroimaging-all had extensive pontine/extrapontine myelinolysis

Achinger, SG Nephrol Dial Transp 2014; 29:2310
Table 1. Group 1 patients, DDAVP withheld during management of hyponatremia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age/gender</th>
<th>Serum sodium</th>
<th>Development of hyponatremia</th>
<th>Clinical presentation</th>
<th>Treatment</th>
<th>Neuroimaging</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Willebrands disease</td>
<td>31/F</td>
<td>143</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Headache, nausea, lethargy</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>28/F</td>
<td>138</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Headache, nausea, lethargy</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Von Willebrands disease</td>
<td>32/F</td>
<td>138</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Seizures, coma</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>18/M</td>
<td>117</td>
<td>Initial</td>
<td>As initial presentation</td>
<td>Seizures, coma</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>59/M</td>
<td>119</td>
<td>Initial</td>
<td>As initial presentation</td>
<td>Seizures, coma</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>37/F</td>
<td>116</td>
<td>Initial</td>
<td>As initial presentation</td>
<td>Seizures, coma</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>35/F</td>
<td>142</td>
<td>Initial</td>
<td>As initial presentation</td>
<td>Dizziness, vomiting</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>56/F</td>
<td>114</td>
<td>Initial</td>
<td>As initial presentation</td>
<td>Dizziness, vomiting</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Von Willebrands disease</td>
<td>22/M</td>
<td>140</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Headache, vomiting, respiratory arrest</td>
<td>0.9% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>28/F</td>
<td>136</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Hallucinations, seizure, respiratory arrest</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>13/F</td>
<td>136</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Seizures</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>26/F</td>
<td>140</td>
<td>Initial</td>
<td>Received hypotonic fluids and DDAVP</td>
<td>Confusion, emesis, respiratory arrest</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>37/F</td>
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<td>As initial presentation</td>
<td>Hypotonic fluids and DDAVP</td>
<td>Confusion, emesis, respiratory arrest</td>
<td>3% NaCl + holding DDAVP</td>
<td>Extrapontine and pontine demyelination</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>32.5/85% F</td>
<td>129.2 ± 13.8</td>
<td>110.3 ± 6.4</td>
<td>147 ± 10.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Management—continue desmopressin, treat with hypertonic saline
Cirrhosis

- Very difficult to manage as there is no real therapy to reverse the vasodilatation of cirrhosis
- Ensure that progressive hyponatremia is not due to volume depletion (re diuretics, lactulose)
- Successful management of HRS w albumin/vasoconstrictors has improved hyponatremia
- Tolvaptan has black box warning in cirrhosis (though 1-2 doses will not be an issue)
- OLT patients have a significant risk of ODS, even when starting Na is >130 (owing to large intra-operative increases in Na)
- Would want Na >125-130 prior to going to the OR
- Options in pre OLT cirrhotic-tolvaptan (if urine volume adequate) vs 3% saline and Lasix vs renal replacement in those who are oliguric
Heart Failure

- Occurs when CI is low, often BP is low
- Thus can be seen in severe systolic HF, severe AS w low CO, infiltrative/restrictive CM w preserved LV function but RV dysfunction and low CO
- Ideal treatment is optimization of CO
- Diuretics can reduce venous congestion and improve GFR which aids in treatment of hyponatremia (also reduce uosm)
- Excessive diuresis can cause hyponatremia
- Tolvaptan is an option
- Rarely can see rapid correction when CO is significantly increased w inotropes
- Afterload reduction w ACEI has been shown to improve hyponatremia in systolic HF
Adaptation

• Acute adaptation involves loss of Na, Cl from brain ECF via bulk flow to CSF-occurs in minutes and complete by ~6hrs
• As a result of brain adaptation, brain swelling is significantly less than predicted for any degree of hyponatremia
• Loss of intracellular solute (K) begins at 3-6 hours and is complete by 48 hrs
• Brain osmolytes (myo-inositol, aminoacids, etc) are significantly decreased by 24 hrs and nearly completely lost by 48 hours
• Adaptation to hyponatremia is ~70% by loss of electrolyte and 30% by loss of osmolyte
Adaptation

• When hyponatremia is corrected, cells take up the solute that was initially lost
• Na, Cl uptake is complete by 48hrs
• K uptake is complete by 48 hours
• Osmolyte reuptake requires 5-7 days; as a result, if Na correction is too rapid the brain will not be able to accumulate enough solute to prevent brain shrinkage.
• Rapid correction of chronic hyponatremia results in overshoot of brain Na,Cl
Pathogenesis of ODS

Rapid correction of severe hyponatremia

Relower Na ☞ Slow reaccumulation of Organic osmolytes

Osmotrauma → Breakdown of BBB → microglial infiltration → cytokine release → demyelination

↑ steroids

↑ Statins, minocycline
6300meq TB Na

\[
\frac{6300\text{ meq}}{45\text{ L}} = 140\text{ meq/L}
\]

100meq 3NaCl% or 50meq NaHCO3

\[
\frac{6400\text{ meq}}{45\text{ L}} = 142\text{ meq/L}
\]

SIADH Uosm = 600mosm/L

6300meq TB Na

\[
\frac{6300\text{ meq}}{49\text{ L}} = 128\text{ meq/L}
\]

1L NS (300mosm/L)

\[
\frac{6300\text{ meq}}{49.5\text{ L}} = 127\text{ meq/L}
\]

300mosm 300osm excreted in 500cc

\[
\frac{600\text{ mosm/kg}}{500\text{ cc}} = 120\text{ mosm/kg}
\]

Hypovolemia, Uosm 300

Urine Na 20

5175meq TB Na

\[
\frac{5175\text{ meq}}{45\text{ L}} = 115\text{ meq/L}
\]

2L NS 300meq Na

\[
\frac{5325\text{ meq}}{41.5\text{ L}} = 128\text{ meq/L}
\]

Vasopressin supressed Uosm 50

3.5L water excreted in 6hrs

150meq Na reabsorbed
Figure 1 Effect of TIVC constriction on $U_{\text{osm}}$ (above) and $C_{\text{H}_2\text{O}}$ (below) in intact (left), hypophysectomized (middle), and baroreceptor-denervated animals (right). The denervated and innervated kidneys are denoted by dashed and solid lines, respectively. Only the 8 experiments are plotted in the intact group in which renal venous and arterial pressures were maintained constant throughout the experiment.
Figure 2: Linear correlation between urine flow rate and $C_{\text{H}_2\text{O}}$ during control and TIVC constriction periods in hypophysectomized animals undergoing a water diuresis. The open and closed circles denote the results from the group II experiments while the open and closed triangles denote the results from group III experiments. In both groups, the open symbols represent the control collections while the closed symbols represent the experiment collections during TIVC constriction.
Effects of ADH and solute excretion on the urine output

Both lower ADH levels and increased solute excretion raise the urine output. It is assumed that the urine osmolality is 70 mosmol/kg in the absence of ADH and 1400 mosmol/kg with maximum ADH effect.
Table 3 Univariable predictors of reversal of herniation.

<table>
<thead>
<tr>
<th>Table 3 Univariable predictors of reversal of herniation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Reversal of TTH</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Age, y 52.1 ± 14.1</td>
</tr>
<tr>
<td>Hyperventilation 41/57 (71.9)</td>
</tr>
<tr>
<td>Propofol use 40/57 (70.2)</td>
</tr>
<tr>
<td>Mannitol use 26/57 (45.6)</td>
</tr>
<tr>
<td>Pentobarbital use 10/57 (17.5)</td>
</tr>
<tr>
<td>2%/3% saline use 26/57 (45.6)</td>
</tr>
<tr>
<td>1-h Na &gt;145 43/56 (76.8)</td>
</tr>
<tr>
<td>1-h Na increase &gt;5 46/54 (85.2)</td>
</tr>
<tr>
<td>Surgical decompression 10/57 (17.5)</td>
</tr>
<tr>
<td>Ventriculostomy 16/57 (28.1)</td>
</tr>
<tr>
<td>Diagnosis of ICH 19/57 (33.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

*Included in multivariable logistic regression model.

TTH = transtentorial herniation; ICH = intracerebral hemorrhage.

Koenig M et al. Neurology 2008;70:1023-1029
No Vasopressin Present
Case

- 82F w HTN who presents with altered mental status and falls in the context of 6 days of nausea, vomiting, diarrhea
- AF, 121/52, 70, 18, 98% room air. Mental status-awake, conversant, delirious. Flat neck veins, lungs, clear, no edema.
- BMP 106 4.3 77 25 7 0.6 gluc 109
- 2L saline→Na 108
- Uosm 340→319
- Urine Na 102
- Tsh/cortisol normal
• Day 2% saline Na 108→113 with fluctuations and requirement of intermittent boluses of NaHCO3 to sustain Na; i/o 1000/2800
Table 1. Principal causes and underlying mechanisms of drug-induced SIAD

<table>
<thead>
<tr>
<th>Increased hypothalamic vasopressin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>antidepressants</td>
</tr>
<tr>
<td>SSRIs</td>
</tr>
<tr>
<td>serotonin and norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>tricyclics</td>
</tr>
<tr>
<td>monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>antipsychotic agents</td>
</tr>
<tr>
<td>phenothiazines</td>
</tr>
<tr>
<td>butyrophenones (haloperidol)</td>
</tr>
<tr>
<td>antiepileptic drugs</td>
</tr>
<tr>
<td>carbamazepine</td>
</tr>
<tr>
<td>oxcarbazepine</td>
</tr>
<tr>
<td>sodium valproate</td>
</tr>
<tr>
<td>anticancer agents</td>
</tr>
<tr>
<td>vincristine and vinblastine</td>
</tr>
<tr>
<td>intravenous cyclophosphamide</td>
</tr>
<tr>
<td>melphalan</td>
</tr>
<tr>
<td>ifosfamide</td>
</tr>
<tr>
<td>methotrexate</td>
</tr>
<tr>
<td>opiates</td>
</tr>
<tr>
<td>miscellaneous</td>
</tr>
<tr>
<td>IFN-α and -γ</td>
</tr>
<tr>
<td>levamisole</td>
</tr>
<tr>
<td>pentostatin</td>
</tr>
<tr>
<td>mAb</td>
</tr>
</tbody>
</table>

Potentiation of vasopressin action on the collecting duct

| antiepileptic drugs                          |
| carbamazepine                                |
| lamotrigine                                   |
| intravenous cyclophosphamide                 |
| antidiabetic drugs                            |
| chlorpropamide                                |
| tolbutamide                                   |
| nonsteroidal anti-inflammatory drugs          |

Direct antidiuretic action

| desmopressin (DDAVP)                          |
| oxytocin (Pitressin)                          |
• Day 3 tolvaptan-Na 113→121 in 8 hours, then remained stable at 121 for the next 16 hours
• i/o 15.5L/16.5L (required massive volumes of D5W→hyperglycemia→insulin gtt)
• UOSM 319→44, urine Na <20, urine K 3
• Day 4-2% saline +furosemide 20mg po bid
• Uosm 174, Una 65
• Na 119→127
Summary of NaCl and H2O transport throughout the nephron during an antidiuresis and a water diuresis

The tubular fluid and interstitial concentrations are expressed in milliosmoles per kilogram (mosmol/kg;) the large, boxed numbers represent the percentage of the glomerular filtrate remaining in the tubule at each site. Note that the composition and volume of the tubular fluid are essentially the same at the end of the loop of Henle as the excretion of a concentrated or dilute urine is determined primarily in the collecting tubules.
Importance of osmolytes in the pathogenesis of ODS

• Areas of the brain with the slowest re-uptake of osmolytes demonstrate the greatest degree of demyelinating lesions in the rat 
  Lien JCI1995;95:1579

• Rapidly corrected azotemic rats reaccumulated 100% of osmolytes at 24hrs compared to 75% in non-azotemic rats. Compared to azotemic rats, non-azotemic rats develop more demyelinating lesions when chronic hyponatremia is rapidly corrected 
  Soupart JASN 2002; 13:1433

• Rapid correction of chronic hyponatremia w urea as compared to lixivaptan or hypertonic saline resulted in fewer demyelinating lesions and neurologic injury in rats 
  Gankam Kid Intern 201587:323

• Administration of myo-inositol to chronically hyponatremic rats prior to rapid correction reduced the number of demyelinating lesions compared to placebo treated rats 
Osmolality vs tonicity

• Osmolality is the measurement of all osmoles in the serum
• Tonicity is the concept of effective osmoles in the serum
• Effective osmoles are restricted to a compartment (cannot freely diffuse from ICF to ECF)
• Na, Cl are the major ECF osmoles
• Urea is an osmole, but it diffuses slowly across cells and thus generates no osmotic force**
• In ESRD BUN can be 100, Na 130-the serum osmolality is increased, but the patient is hypotonic