HPI: 59 year old woman with a past medical history of hypertension presented to the ER with a 5 day history of progressive weakness
Unable to ambulate 2 days prior to admission
ROS: Nausea, paresthesias in hands/feet
Denied vomiting, drug, or laxative use

Medications on Admission:
- Simvastatin 5mg daily
- Losartan/HCTZ 50/12.5mg daily
- Desloratadine
- Augmentin 500mg bid x 2 days for sinusitis
- Naproxen 220mg bid

Pertinent Physical Examination:
Vitals: Temp 97.8 HR 60 BP 143/67
- O2 Sat 99% RA Wt 73 Kgs.
- Orthostatics lying 143/67 59 standing 121/103
- HR 60-129
General: Tired-appearing, slurred speech
Neuro: Alert and oriented x 3, CN II-XII intact, sensation diminished to light touch, motor strength below.
Dysmetria R>L. Gait not tested

Admission Laboratories

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>96 mEq/L (96 mmol/L)</td>
</tr>
<tr>
<td>K</td>
<td>1.6 mEq/L (1.4 mmol/L)</td>
</tr>
<tr>
<td>Cl</td>
<td>&lt;6 mEq/L (0.8 mmol/L)</td>
</tr>
<tr>
<td>HCO3</td>
<td>30 mEq/L (30 mmol/L)</td>
</tr>
<tr>
<td>BUN</td>
<td>11 mg% (0.9 mmol/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.5 mg% (44 μmol/L)</td>
</tr>
<tr>
<td>Glucose</td>
<td>156 mg% (8.7 mmol/L)</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>201 mOsm/L</td>
</tr>
<tr>
<td>Ca</td>
<td>8.4 mg% (2.1 mmol/L)</td>
</tr>
<tr>
<td>Mg</td>
<td>1.9 mg% (0.78 mmol/L)</td>
</tr>
<tr>
<td>P</td>
<td>1.8 mg% (0.58 mmol/L)</td>
</tr>
</tbody>
</table>

EKG: SB 56bpm, LAD, QTc 587
CXR: No acute disease, no infiltrate or effusion
Electrolytes checked 6 months ago - WNL
**Hospital Course**

**Nephrology Consultation**
- Free H2O restriction <800cc/day
- Avoid isotonic or hypertonic solutions
- KCl repletion ~450meq in the next 24hrs to correct hypokalemia

24 h urine volume 3 L
- $U_{Na} = 22$ mm/L, $U_{K} = 48$ mm/L,
- $U_{osm} = 546$ mOsm/Kg

---

**Audience Question**

**This approach will:**

A. Restore K losses but leave serum Na unchanged
B. Result in decrease in serum Na because there is Na in the urine but none is given
C. Result in desired increase in serum Na by 0.5mm/L/h
D. Exceed the desired increase in serum Na by 0.5mm/L/h

---

**Serum [Na+]**

\[
96 \text{ mM/L} = \frac{3504}{73 \times 0.5}
\]

**Solute Balance**

<table>
<thead>
<tr>
<th>Solute</th>
<th>In (mM)</th>
<th>Out (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>K</td>
<td>430</td>
<td>132</td>
</tr>
</tbody>
</table>

Net + 277 mM/d

**Water Balance**

- Oral 800 mls
- Urine 3,060 mls
- With NaCl 300 mls
- Insensible 500 mls
- 1100 mls
- 3560 mls

Net -2.46L/D

---

**Resulting Serum Na**

\[
Na = \frac{3504 + 277}{36.5 - 2.5} = \frac{3781}{34.0} = 111 \text{ mM/L}
\]

Change in 24hrs = 15 mM/L

---

**Mechanism for Increase in Serum Sodium with Potassium Repletion**

- Potassium repletion results in a shift of sodium from the cell with the commensurate entry of potassium into the cell
Hospital Course

Hospital Days #1 - 7:
- No saline or sodium repletion
- Patient received 430 meq of KCl in the first 24 hr
- Serum sodium increased by 15 mM/L in the first 24 hr
- Potassium increased from 1.6 to 5.1 mM/L in the first 24 hr
- Improved metabolic derangements, resolved metabolic alkalosis
- Clinical improvement in motor strength and dysarthria

Hospital Course

- Hospital Day #8
- 8am - Patient alert, anticipating d/c home
- 10am - Nurse assessed patient on routine rounds
  - alert and scared, blank stare
  - unable to verbally respond or follow commands
  - mute, pupils reactive, flaccid throughout with strength 2/5
  - “locked-in syndrome”
- Neurology Consultation called
- Psychiatry Consultation called

MRI Hospital Day #22

MRI brain

The role of neutral amino acid transporter SNAT2

- SNAT2 is up regulated by hypertonicity
- SNAT2 is down regulated by hypotonicity
- This prevents an increase in amino acid transport delaying cell volume recovery

Solute losses in the adaptation to chronic hyponatremia

- Glutamate
- Creatinine
- Taurine
- Inositol
- Glutamine
- Other
- Na+
- K+
- Cl-

Effect of increasing [Na+] on brain water content

From Verbalis et al… in HYponATREmic rats
From Cserr et al… in NORMOnATREmic rats

Plasma [Na+] (mEq/L)

Brain Water Content (ml/100 g DW)
Minocycline Prevents Osmotic Demyelination Syndrome by Inhibiting the Activation of Microglia

Minocycline Protects Against Neurologic Complications of Rapid Correction of Hyponatremia

Minocycline reduces mortality and morbidity after rapid correction of chronic hyponatremia.

Proposed Mechanism
Disruption of B-B Barrier
Microglial Activation          Minocycline
Proinflammatory Cytokines
Demyelination

“Whether minocycline will add anything to our approach to treating hyponatremia will need more studies with designs similar to the clinical setting of an inadvertent rapid correction of chronic hyponatremia and with doses of minocycline that can be safely used in humans.”
Kamel and Halperin

Follow-up Data
Astrocytes Are an Early Target in Osmotic Demyelination Syndrome
**Goal**

To describe the long term prognosis of patients with central or extrapontine myelinolysis

**Method**

Retrospective observational study
46 French intensive care units
36 patients with central pontine or extrapontine myelinolysis

**Results (n=36)**

86% of patients were alcoholics
At one year:
11/36 patients died
25/36 patients alive
14 of these returned to a Rankin score ≤ 1.

**Conclusion**

The prognosis of critically ill patients with central or extrapontine myelinolysis is better than thus far thought despite initial severe clinical manifestations.
Outcomes in ODS

N= 24
favorable outcome 63%

N= 25
favorable outcome 46%

Factors Predicting Prognosis in ODS

- Better GCS (Glasgow Coma Scale) score
- Better in hospital functional scales
- Less severe hyponatremia


Case 2

A 23-year-old woman with her first pregnancy is admitted for induction of labor at 40 weeks gestation for oligohydramnios. Her pregnancy was uneventful. For the past two weeks she had complained of constant thirst, and was consuming 8–10 liters of water per day. She had to urinate every 1-2 hour throughout the day and night. Her fasting glucose is normal, and her urinalysis is negative for glucose.

12 hours after admission fetal distress ensues and she undergoes cesarean section under spinal anesthesia with uneventful delivery.

Postoperatively, she is NPO. One day after delivery, she complains of severe thirst. She develops progressive agitation, confusion, and finally delirium. Her urine output over the past 24 hours is 4.5 liters. Physical examination reveals BP 100/60, pulse 105, flat neck veins, benign abdominal examination, and is otherwise unremarkable.

Laboratory Data

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>172 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>3.6 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>141 mEq/L</td>
</tr>
<tr>
<td>CO₂</td>
<td>23 mM/L</td>
</tr>
<tr>
<td>BUN</td>
<td>14 mg/dl</td>
</tr>
<tr>
<td>Cr</td>
<td>1.5 mg/dl</td>
</tr>
<tr>
<td>Calcium</td>
<td>10.0 mg/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1 g/L</td>
</tr>
<tr>
<td>Serum Osmolality</td>
<td>356 mOsm/kg</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>205 mOsm/kg</td>
</tr>
</tbody>
</table>

What Is the Most Likely Cause of the Hypernatremia?

A. Osmotic diuresis
B. Central diabetes insipidus
C. Nephrogenic diabetes insipidus
D. None of the above

Audience Question
A. Osmotic diuresis

There’s no evidence for osmotic diuresis as the urinary osmolality is lower than plasma osmolality.

Osmotic diuresis are characterized by isotonic or hypertonic urine.

B. Central Diabetes Insipidus

Massive postpartum bleeding can lead to pituitary insufficiency but no such event occurred in this patient making it an unlikely answer. Nonetheless this possibility needs to be ruled out.

C. Nephrogenic diabetes insipidus

Patient has none of the metabolic or drug related causes for acquired nephrogenic diabetes insipidus making this an unlikely cause of the patient’s polyuria.

A. Measure vasopressin level

Vasopressin levels are not readily available in the timeframe required for managing the patient.

The absence of measurable levels would not differentiate central diabetes insipidus from gestational diabetes insipidus

B. Central Diabetes Insipidus

Massive postpartum bleeding can lead to pituitary insufficiency but no such event occurred in this patient making it an unlikely answer. Nonetheless this possibility needs to be ruled out.

C. Nephrogenic diabetes insipidus

Patient has none of the metabolic or drug related causes for acquired nephrogenic diabetes insipidus making this an unlikely cause of the patient’s polyuria.

A. Measure vasopressin level

Vasopressin levels are not readily available in the timeframe required for managing the patient.

The absence of measurable levels would not differentiate central diabetes insipidus from gestational diabetes insipidus

C. 2 micrograms of desmopressin (DDAVP) subcutaneously and urine osmolality

A response to DDAVP would not differentiate gestational diabetes insipidus from central diabetes insipidus.

In both DDAVP would significantly increase urinary osmolality.
D. 5 units of vasopressin subcutaneously and urine osmolality

Failure to respond to vasopressin would not differentiate gestational diabetes insipidus from nephrogenic diabetes insipidus.

In neither of these two disorders would urinary osmolality significantly increase after vasopressin administration.

Gestational D.I.

- Occurs in 1 of 300,000 pregnancies
- Frequently associated with pre-eclampsia
- Consider associated subclinical neurogenic or nephrogenic D.I.
- Consider hepatic dysfunction


Case 3

A 74 year old male with a history of heart failure is admitted with increasing shortness of breath. He is treated with lisinopril 20mg/d, furosemide 20 mg bid and digoxin 0.25 mg/d. On exam BP 145/90 mmHg P.R.: 88/m RR 24/m, O2 sat. 90% on 2L. His Scr is 1.8 mg % and his electrolytes are normal. He is placed on a sodium restricted diet, on fluid restriction and his furosemide is increased to 40 mg bid. The next day on exam he has persistent rales in both lung fields

His laboratory exam reveals:

- Scr: 1.8 mg/dl
- BUN: 25 mg/dl
- Na: 147 mm/lt
- K: 3.7 mm/lt
- CO2: 26 mm/lt
- Cl: 120 mm/lt
Audience Question

Which of the following factors best explains this patient’s hypernatremia?

A. An age related decrement in vasopressin release
   
   For any change in plasma tonicity vasopressin release is actually increased in older individuals.

B. An age related defect in urinary dilution
   
   Free water excretion is decreased with aging most likely as a consequence of decreasing GFR. This should however make the elderly more prone to develop hyponatremia.

   There is a mild defect in maximal urinary concentrating ability with aging.

C. The administration of a loop diuretic in the face of dietary water restriction.

D. An age related decrease in the proportion of body fat to body water.
   
   The proportion of body fat to body water increases with age.

Risk factor for development of severe hypernatremia

- Elderly or Infants
- Hospitalized Patients Receiving
  - Hypertonic Infusions
  - Tube Feedings
  - Osmotic or Loop Diuretics
  - Lactulose
- Altered mental status
- Uncontrolled diabetes mellitus
- Underlying polyuric disorder

Hypernatremia in the ICU

All ICU Admissions n = 389

- Hypernatremia n=56
- On Admission 34
- Hospital Acquired 22
- Time to correction (hrs) 16
- Days in ICU 4.6
- Mortality (%) 12

Polderman K et al. Critical Care Med. 27:1105, 1999
Characterization of Intensive Care Unit Acquired Hyponatremia and Hypernatremia Following Cardiac Surgery

N = 6,770 patients
Hyponatremia developed in 5%


In view of the increased serum sodium urinary data was obtained

<table>
<thead>
<tr>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr: 1.8 mg/dl</td>
<td>Uosm: 392 mOsm/kg</td>
</tr>
<tr>
<td>BUN: 25 mg/dl</td>
<td>UNa: 59 mM/L</td>
</tr>
<tr>
<td>Na: 147 mM/L</td>
<td>UK: 32 mM/L</td>
</tr>
<tr>
<td>K: 3.7 mM/L</td>
<td>Volume: 2.5 Ls</td>
</tr>
<tr>
<td>CO2: 26 mM/L</td>
<td></td>
</tr>
<tr>
<td>Cl: 120 mM/L</td>
<td></td>
</tr>
</tbody>
</table>

Goal
To prevent further increase in serum sodium and achieve negative sodium balances

Answer A
The administration of 0.45% NaCl at cc/cc will restore the water losses but the Na is not desirable in the hypervolemic patient

Patients With Acquired Hypernatremia Have Increased Mortality

<table>
<thead>
<tr>
<th>Measure: Deviation From the Normal Serum [Na+] Range</th>
<th>ICU Mortality</th>
<th>Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(125,130]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(130,135]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(135,140]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140,145]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(145,150]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR (95% CI)
ICU Mortality 5.01 (3.30–7.62)
Hospital Mortality 2.26 (1.57–3.26)

Audience Question
Which of the following treatment regimen is most appropriate at this time?

A. 1 cc of 0.45% NaCl per cc of urine
B. 0.5 cc of D5W per cc of urine
C. 0.5 cc of 0.45% NaCl per cc of urine
D. 1 cc of NS per cc of urine
Analysis of water and solute balance

$$[\text{Na}] = \frac{\text{total body sodium} + \text{total body potassium}}{\text{total body water}}$$

In this case:

$$147 \text{ mEq/L} = \frac{?}{67 \text{ Kg} \times 6} = 147 = \frac{5880 \text{ mEq}}{40 \text{ L}}$$

Answer A:

1 cc of 0.45% NaCl per cc of urine

<table>
<thead>
<tr>
<th>Water (lt)</th>
<th>Solute (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In</td>
<td>2.5</td>
</tr>
<tr>
<td>Out</td>
<td>2.5</td>
</tr>
<tr>
<td>Net</td>
<td></td>
</tr>
</tbody>
</table>

There is no change in Na concentration but no negative Na balance is achieved.

Answer C & D

The administration of 0.9% NaCl provides no free water and further Na loads the patient.

Answer C:

0.5 cc of NS per cc of urine

<table>
<thead>
<tr>
<th>Water (lt)</th>
<th>Solute (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In</td>
<td>1.25</td>
</tr>
<tr>
<td>Out</td>
<td>2.5</td>
</tr>
<tr>
<td>Net</td>
<td>-1.25</td>
</tr>
</tbody>
</table>

$$[\text{Na}]^+ = \frac{5880 + 13}{40 - 1.25} = \frac{5893}{38.75} = 152 \text{ mEq/L}$$

Serum sodium will rise and no negative sodium balance was achieved.

Answer D:

1 cc of NS per cc of urine

<table>
<thead>
<tr>
<th>Water (lt)</th>
<th>Solute (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In</td>
<td>2.5</td>
</tr>
<tr>
<td>Out</td>
<td>2.5</td>
</tr>
<tr>
<td>Net</td>
<td>0</td>
</tr>
</tbody>
</table>

$$[\text{Na}]^+ = \frac{5880 + 200}{40} = \frac{6080}{40} = 152 \text{ mEq/L}$$

Serum sodium will rise and sodium balance is positive.

Case 4

A 34-year-old long distance runner sought medical attention because she was becoming fatigued. She had secondary amenorrhea since age 22 years. Her serum sodium was found to be 124 mEq/L and a range of 124-131 mEq/L on multiple determinations. TSH and serum cortisol were normal. Chest x-ray was normal. She was a strict ovolactovegetarian. She denied alcohol consumption, use of laxatives or diuretics. Her medications included vitamin C, calcium carbonate and prenatal vitamins. Physical examinations revealed a well-developed white female weighing 51.8 kg. Blood pressure was 100-60 and pulse rate was 52. No orthostatic changes. No edema. Neurologic examination was normal. She was admitted for further examination.
Laboratory Findings

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>130 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>4.2 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>92 mEq/L</td>
</tr>
<tr>
<td>CO₂</td>
<td>28 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>6 mg%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 mg%</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>66 mg%</td>
</tr>
<tr>
<td>Posm</td>
<td>268 mOsm/kg</td>
</tr>
</tbody>
</table>

A 24 hour urine collection revealed:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mls/24hrs)</td>
<td>4010</td>
</tr>
<tr>
<td>Uosm (mOsm/kg)</td>
<td>81</td>
</tr>
<tr>
<td>U₅₆ (mEq/L)</td>
<td>10</td>
</tr>
<tr>
<td>U₅₉ (mEq/L)</td>
<td>10</td>
</tr>
<tr>
<td>Urea nitrogen (g/d)</td>
<td>2.45</td>
</tr>
</tbody>
</table>

Audience Question

The best therapeutic approach to the hyponatremia in this patient is

A. Demeclocycline 600mg/d
B. Urea 30g bid
C. Tolvaptan 30mg/d
D. Limit water intake to less than 5 lts/d

A. Demeclocycline 600mg/d

The demeclocycline is used in the treatment of hyponatremic disorders. It antagonizes the action of vasopressin at the tubular level. This patient already has a urinary osmolality < 100 mOsm/kg and therefore no significant benefit would be obtained.

C. Tolvaptan 30mg/d

Tolvaptan is an orally active specific V2 antagonist. It would not be expected to correct hyponatremia in a patient with dilute urine and presumably absent vasopressin levels.

D. Limit water intake to less than 5 lts/d

Severely limiting water intake in this patient would low solute excretion may be therapeutic but intakes in the 4-5 liters per day range that are readily excreted in the face of normal solute intake may be excessive when solute intake is limited.
Patient's Solute Excretion

Solute excretion = V x Uosm
4L X 81 = 320 mosm/day

Source of solutes:

- Na+ intake 40 mM x 2 = 80
- K+ intake 40 mM x 2 = 80
- Obligatory urea excretion 50 mM 50
- Urea 110 mM 110

Protein intake must be very low because we excrete approximately 50mM of urea for every 10 grams of protein intake

Daily Protein Intake =

(UUN +NUN) x 6.25
(UUN + wt x .03) x 6.25
[2.45 + (51.8 x .03)] x 6.25
(2.45 + 1.54) x 6.25 = 25 gm/d

Quantitative Assessment of the Role of Solute Intake on Free Water Generation

V = CH2O + Com

C_{H2O} = V - Com

Com = \frac{U_{osm} V}{P_{osm}}

C_{H2O} = V \cdot \frac{U_{osm} V}{P_{osm}}

Free Water Clearance

C_{H2O} = V \left( 1 - \frac{U_{osm}}{P_{osm}} \right)

In this patient maximal free water excretion:

C_{H2O} = \frac{Solute excretion (1 - U_{osm})}{U_{osm}}

Thus, cH2O = \frac{Solute excretion (1 - U_{osm})}{P_{osm}}

C_{H2O} = 2.8 L/day
Maximal Free Water Excretion at Three Different Rates of Solute Excretion

**Hyponatremia**

- Conversely, increasing solute intake can be used in the treatment of hyponatremia
- Question: How does increasing solute provide such a therapeutic benefit?

Assume patient with SIADH with a fixed urine osmolality of 700 mOsm/kg.

Sodium intake 150 mEq/day

K intake 50 mEq/day

Protein intake 50 g/day \(\rightarrow\) 300 mmol urea

Total solute excretion \(\approx\) 700 mOsm/day

\[
C_{H_2O(e)} = V \left( 1 - \frac{U_{Na} + U_K}{P_{Na}} \right)
\]

\[
C_{H_2O(e)} = 1 \left( 1 - \frac{150 + 50}{120} \right)
\]

\[
C_{H_2O(e)} = - 0.66 \text{ L/day}
\]

Since \(V = \text{solute excretion} \div \text{urine osmolality}\)

\[
V = 1 \text{ Liter} = \frac{700 \text{ mOsm}}{700 \text{ mOsm/kg}}
\]

Question: What is this patient’s electrolyte-free water excretion?

\[
CH_2O(e) = \frac{V}{P_{Na}}
\]
Provide urea to double solute excretion to 1400 mOsm/day
This will double urine output to 2 Liters thereby lowering the concentrations of Na and K

\[ C_{\text{H2O}}(t) = 2 \left( 1 - \frac{75 + 25}{120} \right) \]

\[ C_{\text{H2O}}(t) = +0.34 \text{ L/day} \]
This will increase serum sodium concentration if water intake is not excessive

Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH

SOUPART A. ET AL.
CLIN J SOC NEPHROL 7:742-747, 2012

Goal
To compare the efficacy, tolerability and safety of vasopressin antagonist with those of urea.

Methods
SIADH patients (n=12) treated with vaptans for one year followed by an 8 day washout period and then placed on oral urea for an additional year

Statistics: analysis of variance (ANOVA)

Conclusion
- Urea and vaptans had similar efficacy
- Tolerance was good and comparable for both treatment modalities
Case 5

A 72 year old man with metastatic lung cancer is admitted to the hospital with hyponatremia. He has no symptoms related to hypotonicity at the time of presentation.

On physical examination he was felt to be euvoletic. He weighs 68Kgs.

Laboratory Evaluation

<table>
<thead>
<tr>
<th>Na</th>
<th>121 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>4 mEq/L</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>2.4 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>110 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>7.7 mg/dL</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>289 mOsm/kg H2O</td>
</tr>
<tr>
<td>Urine Osmolality</td>
<td>964 mOsm/kg H2O</td>
</tr>
<tr>
<td>Urine Na</td>
<td>100 mEq/L</td>
</tr>
<tr>
<td>Urine K</td>
<td>68 mEq/L</td>
</tr>
<tr>
<td>Urine Volume</td>
<td>900 ml/day</td>
</tr>
</tbody>
</table>

Your diagnosis is that the patient likely has SIADH as a result of the lung tumor. Since he is not overly “symptomatic” you prescribe 1L per day fluid restriction as initial management. Two days later the serum sodium has fallen to 117 mEq/L.

He is prescribed Tolvaptan up to 60mgs/d. When his serum Na is unchanged his response to V2 antagonist was tested.

Neither the urinary osmolality nor urine flow were significantly altered by the vasopressin antagonist.

Audience Question

The patient’s failure to respond to the V2 antagonist could be due to each of the following except:

a. Very high levels of vasopressin
b. Significant vasopressin independent diluting defect
c. A loss of function mutation of the V2 receptor
d. Excessive concomitant water intake
e. Gain of function mutation of the V2 receptor

A. Very high levels of vasopressin

Since tolvaptan is a competitive inhibitor it is conceivable that when hormone levels are very high the drug may not work.
Plasma AVP Levels are Inappropriately Elevated in Most Patients with SIADH

B. Significant vasopressin independent diluting defect

While maximal urinary dilution requires the absence of vasopressin, if renal hemodynamics are markedly altered maximal dilution is impaired even in the absence of vasopressin

Response to Tolvaptan is blunted in cirrhosis

D. Excessive concomitant water intake

While water intake can be liberalized in patients receiving V2 antagonists, excessive water intake can blunt the response

E. Gain of function mutation of the V2 receptor

If the vasopressin receptor is activated in the absence of the hormone the antagonist will be ineffective

Nephrogenic SIAD

Caused by an activating mutation of the AVP V2R at the same site that also can cause DI via an inactivating mutation
Nephrogenic Syndrome of Inappropriate Antidiuresis in Adults

- 74 yr old man found not responsive to satavaptan or tolvaptan

Familial Nephrogenic Syndrome of Inappropriate Antidiuresis: Dissociation Between Aquaporin-2 and Vasopressin Excretion

Ranchin B et al. J Clin Endocrinol Metab. 2010;95(9):E37-E43.

Patients

Included in analyses:
- 2 young brothers, their mother, and her 2 sisters
- Age-matched controls (n=7)

Responses to Water Load in 3 Heterozygous Carriers for the Mutated V2R

Conclusion

Adult carriers may be prone to hyponatremia

Case 6

54-year-old alcoholic admitted after falling at home and breaking elbow
- No prior medical history
- Drank one case beer/day, no other medications
- Exam: Afebrile BP 80/50, unable to maintain upright posture. Lethargic, but no focal finding. No edema.
**Goal**

- To prevent further increase in serum sodium, yet restore ECF volume

<table>
<thead>
<tr>
<th>Blood</th>
<th>Admission</th>
<th>2 hrs</th>
<th>6 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na] mEq/l</td>
<td>106</td>
<td>114</td>
<td>120</td>
</tr>
<tr>
<td>[K] mEq/l</td>
<td>2.7</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>[Cl] mEq/l</td>
<td>87</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>[CO2] mEq/l</td>
<td>33</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Creat mg %</td>
<td>0.6</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>BUN mg %</td>
<td>33</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Osm mosm/kg</td>
<td>246</td>
<td>248</td>
<td>249</td>
</tr>
<tr>
<td>Urine Osm</td>
<td>258</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Na] mEq/l</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[K] mEq/l</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>1 L in bladder</td>
<td>150 cc/hr</td>
<td>150 cc/hr</td>
</tr>
<tr>
<td>Therapy</td>
<td>NS 2 L, plus NS 200 cc/hr KCl</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

**Audience Question**

**At the Time the Best Management is:**

A) Fluid restriction to 1000 ccs/d
B) Administer 0.45 % NaCl at cc/cc of urine
C) Administer 0.9 % NaCl at cc/cc of urine
D) Administer 5 % DW at 0.5 cc/cc of urine
E) Administer 0.9 % NaCl at c/c of urine and give dDAVP

**Answer A:**

Water restriction will result in an increase in serum sodium concentration as electrolyte free water is excreted and very little is given. It will not restore ECF volume.

**Answer B:**

0.45% NaCl at cc/cc of urine provides only 75 mls/hr of free water. Since 126 ml/hr are being excreted serum Na will rise.
C) Administer 0.9 % NaCl at cc/cc of urine

Answer C:

0.9% NaCl at cc/cc may restore ECF volume but fails to provide any free water and will result in a rapid increase in serum Na.

D) Administer 5 % DW at 0.5 cc/cc of urine

Answer D:

5% DW at 0.5 cc/cc provides only 75 ml/hr of free water to a patient excreting 126 ml/hr. Thus, the serum Na will rise. Furthermore, this approach will not restore ECF volume.

E) Administer 0.9 % NaCl at c/c of urine and give dDAVP

Answer E:

The administration of dDAVP allowed the excretion of the urine without electrolyte free water and therefore, for the safe infusion of isotonic NaCl in order to restore to total body sodium.


-12 polydipsic patients
(Na < 115 mM/d symptomatic)

7 uneventful recovery
5 neurologic complications

Change in Serum Na

You see a 53 yo man in follow-up whom you have treated for biopsy documented focal and segmental glomerulosclerosis (FSGS). You treated him for 6 months with an ACE inhibitor and prednisone 60 mg per day with good resolution of his edema and weight loss of 3 kg. His urine protein/creatinine improved from 8 to 2.4. On this regimen his blood pressure increased moderately. About a month ago you tapered the steroids but maintained the ACE inhibitor. A week ago he fell on the ice and fractured his right radius.

On exam you note that he has a cast on his right arm. His blood pressure is higher and he has more edema than the last visit. Lungs are clear and there is no JVD. Comparison of lab values from the initial visit show:

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>85 kg</td>
<td>85 kg</td>
</tr>
<tr>
<td>BP</td>
<td>138/90</td>
<td>152/98</td>
</tr>
<tr>
<td>Pulse</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Na</td>
<td>140</td>
<td>139</td>
</tr>
<tr>
<td>K</td>
<td>3.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Cl</td>
<td>108</td>
<td>110</td>
</tr>
<tr>
<td>HCO3</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>BUN</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Urine prot/crea</td>
<td>8.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The most likely cause of his worsening edema is

1. Unsuspected increase in dietary NaCl
2. New onset of heart failure
3. Unsuspected NSAID use prescribed by the orthopedic surgeon
4. Relapse of FSGS
5. Acute hypertension from worsening renal function

Effect of NSAIDS – normal to high Na diet

- In volume replete/expanded state COX 2 synthesis in medullary interstitial cells increases PGE2 synthesis and inhibits NaCl absorption by TALH and collecting duct.
PGE2 inhibits Na absorption

NSAID blocks PGE2 effect

Effect of NSAIDS – low Na diet

- In volume contracted state COX 2 synthesis in macula densa increases PGI2 synthesis and maintains GFR.

NSAID blocks PGI2 effect – volume contraction and/or inflammation

Summary

1. NSAIDS cause Na retention when Na intake is sufficient
2. NSAIDS cause reduction in GFR in volume contracted states, inflamed glomeruli or underperfused kidneys
Disorders of Na Balance

Case 2

ASN Board Review Course

A previously healthy 23 yo woman presented a year ago with sudden onset of edema and fatigue. Kidney biopsy showed minimal change disease. You treated her with prednisone and 6 months later she had minimal proteinuria, normal renal function and no edema. Now she returns with similar symptoms for 6 days. Because she is miserable, she requests therapy that will quickly reduce her edema and fatigue.

Exam shows BP 122/78, P 88, 4+ edema, dullness and decreased breath sounds at both lung bases. No JVD.

You surmise that she has a relapse of her minimal change disease. Her initial response to therapy required over a month of steroids and diuretics before she was able to function normally.

<table>
<thead>
<tr>
<th></th>
<th>6 months ago</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>65 kg</td>
<td>78 kg</td>
</tr>
<tr>
<td>BP</td>
<td>120/82</td>
<td>122/78</td>
</tr>
<tr>
<td>Pulse</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>Na</td>
<td>140</td>
<td>139</td>
</tr>
<tr>
<td>K</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Cl</td>
<td>108</td>
<td>109</td>
</tr>
<tr>
<td>HCO3</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>BUN</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Urine protein/creat</td>
<td>0.3</td>
<td>14.2</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Audience Question

In addition to steroid and ACE inhibitor therapy, the most effective therapy for improving the symptoms of edema in this patient is

1. Admit her to the hospital for constant furosemide infusion
2. Begin bumetanide therapy instead of furosemide as an outpatient
3. Admit her to the hospital for albumin infusion followed by bolus furosemide infusion
4. Initiate spironolactone therapy instead of furosemide as an outpatient
5. Initiate furosemide therapy TID as an outpatient
Mechanisms of diuretic resistance

1. Reduced absorption from GI tract (furosemide)
2. Reduced GFR and nephron mass
3. Effective volume contraction with enhanced Na absorption by other nephron segments
4. Drug interactions – interference with secretion (probenecid, sulfonamide and beta lactam abx, MTX, valproic acid, cimetidine, some antiviral agents)
5. Drug effects to enhance Na absorption – NSAIDS
6. High NaCl intake
7. Hypoalbuminemia

Why does hypoalbuminemia contribute to diuretic resistance?

1. Decreased furosemide binding to albumin
2. Decreased tubular secretion
3. Leak out of intravascular space - increased volume of distribution
4. Increased metabolism to inactive compounds
5. Increased binding of diuretic to albumin in tubular lumen

Mechanism of loop diuretic action

1. filtration
2. secretion (majority)
3. action from the tubular lumen
4. duration of action ~4 h
5. ceiling effect (~100-200 mg furosemide IV for nephrotic syndrome)

Diuretic Resistance


Therapeutic strategies

1. Reduce proteinuria (low protein diet, ACEI, ARB, spironolactone)
2. Reduce Na intake
3. Loop diuretics TID doses more effective than single dose
4. Add other diuretics - K sparing, thiazides, CA inhibitors

Counteracting the compensation

1. Hypertrophy of DCT
2. Hypertrophy of CCD and K secretion
3. Enhanced proximal absorption
Diuretic strategy for persistent edema

1. Loop diuretics
2. K-sparing diuretics
3. Thiazide diuretics
4. Prox tubule – acetazolamide

Summary of therapeutic strategies for treatment of nephrotic syndrome

1. reduce proteinuria (low protein diet, ACEI, ARB, spironolactone)
2. reduce Na intake
3. loop diuretics TID doses more effective than single dose
4. add other diuretics - K sparing, thiazides, CA inhibitors
5. No IV albumin
6. avoid NSAIDS and other interfering drugs
7. switch types of loop diuretic (bumetanide, torsemide)

Disorders of Volume and Water Balance - Case 3
ASN Board Review Course

A 58 yo man was diagnosed with a squamous cell cancer of the tonsils 6 months ago and underwent radiation therapy and cisplatin-based chemotherapy. At the time his electrolytes and renal function were normal (creat = 0.8). During the second round of chemotherapy, he developed acute kidney injury (creat = 4.3) which was treated conservatively and cisplatin therapy was stopped.

Lab values

| CBC normal  | Na 117 |
| Liver tests | K 4.9 |
| Bilirubin 1.3 | Cl 81 |
| AST 56 (↑) | HCO₃ 24 |
| ALT 42 (↑) | BUN 16 |
| LDH 202 | Cr 1.2 |
| Alk Phos 35 | Posm 256 |
| Albumin 2.8 (↓) | Uosm 128 |
| UNa 46 |

Over the past 3 months he has developed increasing fatigue, decreased appetite, and loss of energy with a 10 pound weight loss. He was admitted for evaluation. Exam showed BP 114/63, P 86, O2 sat 98% on room air, and he appeared comfortable. Lungs clear, no JVD. Tumor mass was greatly reduced, and there was no evidence of metastases.
Audience Question

He was sent home on nutritional supplements and water restriction.

His hyponatremia was from SIADH

1. True
2. False

Lab values

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO3</th>
<th>BUN</th>
<th>Cr</th>
<th>Posm</th>
<th>Uosm</th>
<th>UNa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>11.3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hct</td>
<td>34</td>
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<td></td>
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<tr>
<td>WBC</td>
<td>6.5</td>
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<tr>
<td>Pts</td>
<td>168</td>
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</tr>
</tbody>
</table>

Liver tests:

Not changed

Hgb 11.3
Hct 34
WBC 6.5
Pts 168

1. Plasma vasopressin level
2. 24 h urine for protein, creatinine, and Na
3. Echocardiogram
4. Plasma renin and aldosterone
5. Plasma cortisol

What is the most informative test to order next?

1. Plasma vasopressin level

His Uosm is greater than Posm. He has circulating vasopressin. No need to measure.

2. 24 h urine for protein, creatinine, and Na

Would give some information, but only marginal.

3. Echocardiogram

No evidence of heart disease, and there is Na in the urine. Still a possibility.

What is the most informative test to order next?

4. Plasma renin and aldosterone

A good possibility looking for adrenal insufficiency.

5. AM plasma cortisol

The best single test for adrenal failure.

What is the most informative test to order next?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol</td>
<td>29 (normal 12-24)</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.1 (normal 0.2-1.5)</td>
</tr>
<tr>
<td>Plasma aldosterone</td>
<td>0.3 (normal 2-31)</td>
</tr>
</tbody>
</table>
What is the diagnosis?

A. SIADH
Yes, he has high circulating ADH levels and hyponatremia, but this diagnosis requires that the patient has normal adrenal function (among other requirements).

B. Addison's Disease
His cortisol level is normal, so he does not have Addison's disease, despite the high pre-test probability.

C. Type 4 RTA
Yes, he does have Type 4 RTA – it is a feature of lack of sufficient aldosterone. In this case we can diagnose the cause of Type 4 RTA.

D. Hyporeninemic hypoaldosteronism
The correct diagnosis – an unusual complication of cisplatin therapy.

Most appropriate therapy for this patient

High NaCl diet
Mineralocorticoid therapy (fludrocortisone)

Lab values

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO3</th>
<th>BUN</th>
<th>Cr</th>
<th>Posm</th>
<th>Uosm</th>
<th>UNa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>11.3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hct</td>
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<tr>
<td>WBC</td>
<td>6.5</td>
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<tr>
<td>Liver tests:</td>
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<tr>
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</tbody>
</table>

Causes of isolated hypoaldosteronism

- Congenital
- Heparin (including low molecular weight forms)
- ACE inhibitors
- Atrial natriuretic peptide
- Ideopathic
A 32 yo woman is referred to you for polyuria and polydipsia. She has a 10 year history of bipolar disorder and has been treated with many kinds of medication with only partial success. Three months ago her psychiatrist initiated LiCO3 therapy. She has been having increasing thirst, increasing urine production and enuresis for the past 2 months. You note that 4 years ago her electrolytes and renal function were normal.

On exam she appeared mildly agitated and had difficulty concentrating on simple questions. BP 134/88, P 86. The exam was otherwise unremarkable. There was no edema and no JVD.
The referring physician suspected psychogenic polydipsia and asked your opinion about water restriction to reduce the enuresis.

Lab Exam

<table>
<thead>
<tr>
<th>CBC</th>
<th>AST</th>
<th>ALT</th>
<th>Na</th>
<th>ALT normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>normal</td>
<td>144</td>
<td>K</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cl</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCO₃</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BUN</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creat</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posm</td>
<td>299</td>
</tr>
</tbody>
</table>

Urinalysis

<table>
<thead>
<tr>
<th>Sp Gr</th>
<th>Glucose</th>
<th>Blood</th>
<th>Protein</th>
<th>Leuk esterase</th>
<th>Uosm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.005</td>
<td>neg</td>
<td>neg</td>
<td>trace</td>
<td>neg</td>
<td>146</td>
</tr>
</tbody>
</table>

Audience Question

Is a water deprivation test appropriate?

A. Yes
B. No

How does Li⁺ produce NDI?

Vasopressin Works

Water Deprivation Test

Ann Intern Med 7 February 2006;144 186-194

How does Li⁺ produce NDI?
**Effects of Li+ on Principle Cell**

**Why is the serum creatinine higher than previously measured?**

About 20-30% of patients on chronic Li therapy will eventually show some degree of renal insufficiency. Biopsies usually show interstitial nephritis. The extent to which continued Li therapy might produce further renal injury is unclear.

**Can the effects of Li be explained completely on the lack of production of cAMP in response to vasopressin?**

Li+ inhibits AQP2 protein production in cultured collecting duct cells

![Graph showing Li+ inhibits AQP2 protein production](JASN 17: 1063, 2006)

**Newly Recognized Effects of Li+**

- Decreased AQP2 and AQP3 mRNA and protein
- Decreased expression of urea transporter UT-A1
- Decreased amount of osmolytes and urea in inner medulla
- Inhibition of other enzymes (GSK-3β)
- All of the above are improved with amiloride therapy

Li+ inhibits AQP2 protein and mRNA levels to a much greater extent than it inhibits cAMP levels. Li+ effects are more complex than previously believed.
**Summary – Effects of Lithium on Kidney Function**

1. Almost all patients on Li⁺ will have evidence of nephrogenic diabetes insipidus
2. Li⁺ inhibits cAMP formation by the collecting duct and many other processes
3. Li⁺ enters the principle cell via ENaC and is extruded ineffectively
4. Li⁺ commonly produces interstitial nephritis
5. Amiloride can partially alleviate the effects of Li⁺ on principle cells by blocking entry via ENaC

**Case 5**

- Cynthia L., age 28, began training for the Boston Marathon in 2002 as part of a Leukemia and Lymphoma training team.
- She had finished her PhD in Psychology 4 days prior to the marathon.
- Topic: How running marathons helps family members of cancer patients cope with their loved ones’ illness.
- Initially, she was doing well. Her pace was for a 4 hour marathon finish.
- At mile 22, she began to feel weak.
- At mile 23, she vomited
- 100 yards later, she collapsed.
- EMS personnel were on scene within 5 minutes and she was transferred to the Brigham and Women’s hospital.
- On route she became unresponsive.
- She required 100% face mask oxygen.

**Case**

- In the ER, her initial sodium was 115 meq/L.
- CT of her head revealed the following:

**Amiloride Improves Urinary Concentration in Lithium Treated Patients**

**Amiloride effect on urine osmolality in patients taking Li⁺**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage change in urinary osmolality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li⁺</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Li⁺+A</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>P&lt;0.005</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

**Urine Volume (liters/24hr)**

<table>
<thead>
<tr>
<th></th>
<th>Li⁺</th>
<th>Li⁺+A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>P&lt;0.005</td>
<td>(N=20)</td>
<td>(N=20)</td>
</tr>
</tbody>
</table>

**Urine osmolality (mOsm/kg H₂O)**

<table>
<thead>
<tr>
<th></th>
<th>Li⁺</th>
<th>Li⁺+A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>225</td>
<td>300</td>
</tr>
<tr>
<td>P=0.003</td>
<td>(N=20)</td>
<td>(N=20)</td>
</tr>
</tbody>
</table>

**What is the most appropriate treatment?**

a. NS at 100 ml/hour
b. 3% saline 100 ml boluses
c. ½ NS at 100 ml/hour
d. IV lorazepam
Case

- Over the next 5 hours she progressively deteriorated with the development of fixed, dilated pupils and was declared brain dead at 7:09 pm.

Case

- Cynthia’s kidneys, lungs, heart, cornea were donated.

Marissa A., age 14 received Cynthia’s heart

Exercise Associated Hyponatremia

Severe/Symptomatic Hyponatremia

- Serum [Na+] ≥ 120 mmoi/L or symptoms requires the administration of hypertonic 3% saline.
  - All EAH is acute- hyponatremia can be safely corrected rapidly
  - No cases of osmotic demyelination reported

Severe Hyponatremia

- In the report by Ayus et al:
  - 6 of the 7 patients were treated with 3% saline
  - Increase in [Na+] by 10 mmoi/L in 12 hours
  - Pulmonary and cerebral edema resolved as [Na+] increased
  - One patient had unsuspected EAHE, not treated with hypertonic saline; died of cardiopulmonary arrest from brainstem herniation
  - All 6 patients treated with hypertonic saline recovered and were well after 1 year follow up
  - Although counterintuitive, 3% saline should be used if pulmonary edema and hyponatremia are present


Hypertonic Saline

- In the field:
  - 100 ml of 3% saline
  - Raises serum sodium 2-3 mmoi/L
  - Decreases AVP, enhances intravascular volume (equivalent to 1200 ml of 0.9% saline)

Hypertonic Saline

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  - 100 ml of 3% saline
  - Raises serum sodium 2-3 mmoi/L
  - Decreases AVP, enhances intravascular volume (equivalent to 1200 ml of 0.9% saline)
Hospital-based therapy of EAH

- Continued use of 3% saline recommended
- Usually at a rate of 1-2 ml/min/kg with close monitoring of both serum and urine electrolytes
- In cases of severe antidiuresis, rate may have to be increased to 3-4 ml/min/kg
- In cases of pulmonary edema, use of 3% saline is imperative.

Case 6
A 72-year-old male with HF

- Admitted to hospital with increasing shortness of breath, dyspnea with minor exertion, worsening peripheral edema
- Past medical history
  - Systolic HF with ejection fraction of 25%
  - Type 2 diabetes mellitus
  - Coronary artery disease
  - Hyperlipidemia
- Medications
  - Lisinopril 20 mg daily
  - Furosemide 80 mg twice daily
  - Spironolactone 25 mg daily
  - Carvedilol 25 mg twice daily
  - Atorvastatin 10 mg daily
  - Insulin

Case 6
Physical exam

- Blood pressure: 100/50 mm Hg
- Pulse: 100 bpm, regular
- Jugular venous distention and pulmonary rales noted as well as findings consistent with a right-sided pulmonary effusion
- +3 lower extremity edema

Case 6
Lab values

**Blood**
- Na⁺ 129 mEq/L
- K⁺ 3.5 mEq/L
- Bicarbonate 30 mEq/L
- Chloride 84 mEq/L
- Urea nitrogen 29 mg/dL
- Creatinine 1.2 mg/dL
- NT-BNP 6900 pg/mL

**Urine**
- Na⁺ < 20 mEq/L

Case 6
Hospital course

- Patient started on IV furosemide continuous infusion at 10-20 mg/hr
- Intermittent metolazone 5 mg daily also given
- Urine output significantly increased to 2.2 L/d and weight began to decrease
- However, the serum [Na⁺] values began to fall....
Case 6
Treatment options
What is the best option for treatment of this patient’s volume overload and worsening hyponatremia?

A. 3% HTS infusion
B. Addition of NaCl tablets
C. Tolvaptan 15 mg/d
D. Fluid restriction to < 1 L/d
E. Hold diuretics until sodium increases

Case 6
Discussion of treatment options
• In setting of HF, use of HTS alone will lead to continued volume overload and is not indicated
• NaCl could be used along with a loop diuretic, but is difficult to titrate and risks volume overload
• Fluid restriction to < 1 L is difficult, has negative effects on quality of life, and is slow to take effect
• Tolvaptan is the optimal therapy in this patient because it allows for a predictable rise in [Na⁺], maintenance or improvement in volume status, and can be easily continued in an outpatient setting for up to 30 days

2013 ACCF/AHA Guidelines
• “In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V2 receptor selective or a nonselective vasopressin antagonist.
  • (Level of Evidence: B)”
• -2013 ACCF/AHA Guideline for the Management of Heart Failure


2013 ACCF/AHA Guidelines
• Vaptans
  • Improve serum [Na⁺] in hypervolemic hyponatremia
  • Acutely produce incremental dyspnea relief and incremental weight loss (EVEREST and QUEST trials)
  • Long-term tolvaptan therapy – no improvement in mortality in patients with HF
• •Vaptans - reasonable choices for treatment of hyponatremia in patients with HF with hyponatremia-related cognitive symptoms, or in whom progressive hyponatremia develops when treating with high doses of loop diuretics
  • Long-term outcome data not available

Case 6
Outcomes
• Patient started in the hospital on tolvaptan, 15 mg/d, uptitrated to 30 mg/d
• Urine volume increased, urine osmolality decreased, and serum [Na+] increased by ~4 mEq/L/d over first 48 hours then remained constant
• Patient maintained on tolvaptan as an outpatient with good results with monitoring of liver function tests and then stopped at week 3 post-discharge

Hyponatremia in CHF
• Nearly 1 million hospitalizations for CHF occur annually in the United States1
  − Most are related to worsening systemic congestion1
  − Use of diuretics, the mainstay therapy for congestion, contributes to electrolyte abnormalities and worsening renal function1
• Hyponatremia is common in patients with cardiac disease
  − In a large European study, 20% of patients hospitalized with heart failure had concomitant hyponatremia2
  − Other studies have found as many as 28% of patients hospitalized with CHF had hyponatremia3,4
• Hyponatremia concomitant with CHF significantly increases hospital length of stay (P < 0.0001)5

Na⁺ and Water Retention in CHF
• Na⁺ retention in CHF is primarily mediated by renal mechanisms
  − Decrease in renal blood flow and glomerular filtration rate
  − Increase in tubular reabsorption of NaCl
  − Elevation of renin-angiotensin-aldosterone
  − Inadequate natriuretic mechanisms
• Water retention is a parallel process
  − Obligatory water reabsorption accompanies salt reabsorption
  − Elevated angiotensin II stimulates thirst and provokes release of AVP, the major controller of water reabsorption
  − Reduced renal tubular flow increases free-water absorption
  − Diuretics exacerbate this condition

Hyponatremia and Cardiac Failure

The Pathophysiology of Heart Failure

Non-osmotic Vasopressin Release in Cardiac Failure
**Prevalence of Hyponatremia in HF Patients**


**Negative Correlation of Plasma AVP with Cardiac Index in the Patients with Congestive Heart Failure**

Plasma AVP (pmol/l) vs Cardiac Index (L/min/m²) (Funayama H et al., Kidney Int. 2004;66:1387-1392.)

**Serum [Na+] Over 4 Days After Continuous IV Infusion of Conivaptan**


**Tolvaptan Raises Serum [Na+] in Acute HF Patients (ACTIV Study)**


**All-Cause Mortality and Cardiovascular Mortality or Hospitalization for HF**


**What’s New**

- Diuretic resistance and the use of hypertonic saline
- Neurohormonal upregulation stimulates avid sodium and water reabsorption via angiotensin II, sympathetic nervous system, aldosterone and vasopressin
- DCT hypertrophy in response to loop diuretics
- Impaired diuretic absorption (CHF)
Use of HTS in CHF

- Cardiovascular hemodynamics
  - Increased preload, decreased afterload
  - Positive inotropy
- Neuroendocrine
  - Inhibits RAAS and reduces SNS activity
  - Anti-inflammatory effect (reduce TNFα, IL-6)
- Renal
  - Decreased renal vascular resistance
  - Increased renal blood flow
  - Enhanced distal tubule Na/water delivery

Liszkowski M, Nohria A. Curr Heart Fail Rep 2010; 7: 134

HTS in CHF

- 60 patient with refractory systolic HF
- Randomized to twice daily high-dose IV furosemide or twice daily IV furosemide plus HTS (dose dependent upon baseline serum sodium)
- HTS increased natriuresis and diuresis
- Shortened length of stay by 3 days
- HTS group: GFR improved from baseline while GFR decreased in diuretic only group
- No adverse cardiopulmonary or neurological outcomes
- Several other studies with similar outcomes


Recent Consensus Guidelines: US

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severely symptomatic patient with very low or rapidly falling serum sodium</td>
<td>Hypertonic (3%) saline combined with loop diuretic to prevent fluid overload</td>
</tr>
<tr>
<td>Mild to moderate symptomatic hyponatremia</td>
<td>Initiate fluid restriction (1L/day). Administer furosemide if volume overloaded</td>
</tr>
<tr>
<td>Failure of serum sodium to correct</td>
<td>Lift fluid restriction. Start vaptan therapy</td>
</tr>
</tbody>
</table>


Other consensus recommendations:

- Treat HF-related hyponatremia as chronic and observe correction limits
- Consider discontinuation of treatment when:
  - Serum sodium has normalized
  - Symptoms are improved
  - Serum sodium is not compromising use of diuretics
- Post-discharge assessment of chronic hyponatremia
  - Therapy holiday may be helpful in assessing need for chronic therapy 2-4 weeks after initiation of therapy


Guidelines-European Best Practice

- Recommended against vaptan use
- Rationale:
  - Modest rises in serum sodium levels
  - No significant reduction in mortality
  - Risk for overly rapid correction (although no cases of osmotic demyelination)
  - Recent concerns from PKD trials of risk for liver injury
- Guideline does not specifically give an approach to management of hyponatremia in HF

Case One

A Patient with Liver Disease and Hyponatremia

A 30-year-old woman with type 1 diabetes mellitus and bipolar disorder presents with three weeks of pruritus, pale stools, dark urine and abdominal pain.

Medications include quetiapine, lithium, and insulin.

Physical examination: Scleral icterus, no jugular venous distention, clear lungs, no gallop, no organomegaly, no edema.

Laboratory Data:
- AST 144, ALT 212, Alkaline phosphatase 2056 IU
- Total bilirubin 12 mg/dl
- Na 119 K 4.4 mmol/l
- BUN 12, Creatinine 1.0, Glucose 240 mg/dl
- Plasma osmolality 285 mOsm/kg
- Urine osmolality 434 mOsm/kg
- Urine Na 62 mmol/l
- Total serum proteins 5.1 g/dl
- There is no lipemia and ethanol levels are negative

Which ONE of the following is MOST likely to reveal the cause of the patient’s hyponatremia?
A. Abdominal ultrasound
B. Plasma lithium level
C. Serum triglycerides
D. Serum cholesterol
E. Repeat serum sodium after stopping quetiapine

Goals of the Case
- To recognize pseudohyponatremia and avoid inappropriate therapy
A Patient With Liver Disease and Hyponatremia

Which ONE of the following is MOST likely to reveal the cause of the patient's hyponatremia?
A. Abdominal ultrasound  
B. Plasma lithium level  
C. Serum triglycerides  
D. Serum cholesterol  
E. Repeat serum sodium after stopping quetiapine

Diagnostic Evaluation of Hyponatremia

- Confirm hypotonic hyponatremia
- Exclude thiazides
- Assess volume
  - History and physical
  - Laboratory (urine Na, uric acid, BUN, etc)
  - Response to isotonic saline
- If SIADH, determine the cause


Hyponatremia Without Hypoosmolality

Labs:   Serum Na: 119 mEq/L  
Plasma osmolality:  285 mOsm/kg

Possible causes:
- Increased concentration of non-sodium solutes
  - Endogenous
  - Exogenous
- Pseudohyponatremia

Hyponatremia Due to Extra Solutes

- Endogenous -- Normal osmolar gap
  - High BUN
  - Hyperglycemia
- Exogenous -- Increased osmolar gap
  - Ethanol
  - Methanol
  - Ethylene glycol
  - Isopropyl alcohol or ketoacidosis (acetone)
  - Hypertonic Mannitol
  - IgG infusion (sucrose and maltose)
  - Absorbed irrigants (mannitol, glycerine, sorbitol)
A Patient With Liver Disease and Hyponatremia

Laboratory Data:
- AST 144, ALT 212, Alkaline phosphatase 2056 IU
- Total bilirubin 12 mg/dl
- Na 119 K 4.4 mmol/l
- BUN 12, Creatinine 1.0, Glucose 240 mg/dl,
- Plasma osmolality 285 mOsm/kg
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- Urine Na 62 mmol/l
- Total serum proteins 5.1 gm/dl
- There is no lipemia and ethanol levels are negative

Non-hypotonic hyponatremia

- Calculated osmolality:
  \[ PNa \times 2 + \frac{glucose}{18} + \frac{BUN}{2.8} = 119 \times 2 + \frac{240}{18} + \frac{12}{2.8} = 238 + 13 + 4 = 255 \text{ mOsm/kg} \]
- Measured osmolality
  285 mOsm/kg
- 30 mOsm/kg "Gap"
  - Hyponatremia due to exogenous solutes
  - Pseudohyponatremia

Recognizing Pseudohyponatremia

- Serum sodium concentration by direct potentiometry (blood gas machines) normal
- Any method involving dilution (e.g. indirect potentiometry) gives spurious result
- Most laboratory autoanalyzers use indirect potentiometry

Turchin, NEJM 349(15):1465-9, 2003
Pseudohyponatremia and Hyperlipidemia

- Pseudohyponatremia typically due to increased triglyceride-rich chylomicrons with visible specimen turbidity
  - Direct potentiometry eliminates artifact
  - Ultracentrifugation before indirect potentiometry
- Hypercholesterolemia usually not associated with turbidity or pseudohyponatremia

Hypercholesterolemia due to Lipoprotein X

- Described in severe cholestasis
- Reflux of unesterified cholesterol and phospholipids into the circulation from the cholestatic biliary ducts
- Not soluble in plasma water and thus increases the solid fraction of plasma, causing pseudohyponatremia
- May cause hyperviscosity

Turchin, NEJM 349(15):1465-9, 2003

Pseudohyponatremia & Jaundice

- Lipoprotein X (LpX) may account for high percentage of hypercholesterolemia in cholestatic and obstructive jaundice
- No turbidity of the serum sample
- Associated with pseudohyponatremia

Clin Chem Acta 2006; 366:357

Case Two

A woman with post-operative hyponatremia

Post-Operative Hyponatremia

- A 40-yr-old previously healthy woman weighing 50 kg undergoes surgery for a ruptured ovarian cyst.
- During the operation and in the recovery room, she is given 3 L of lactated Ringer solution.
- After surgery she receives 5% dextrose in 0.45% NaCl with 20 mEq KCl/L at 250 ml/h

Post-Operative Hyponatremia

- On the second post-operative day, she complains of headache and vomiting.
- PE: BP is 140/80 mmHg. She is alert and oriented. No jugular venous distention, clear lung fields and no edema. There are no focal neurological findings.
Post-Operative Hyponatremia

Laboratory data:
- Serum Na: 115 mEq/L
- Plasma osmolality: 241 mOsm/kg of H2O
- Urine osmolality: 850 mOsm/kg of H2O
- Urine sodium: 220 mEq/L
- Urine output is 150 ml/hr

In addition to stopping D5 ½ NS, which ONE of the following would be the most appropriate treatment?
A. No intravenous or oral fluids and observe
B. Conivaptan intravenously
C. 0.9% NaCl 1 liter over 1 hour
D. 3% saline @ 25 ml/hr
E. 3% saline 100 ml over 15 minutes

Goals of the Case

- To develop an effective treatment strategy to prevent the complications of acute hyponatremia

Clinical Features
- Hyponatremia developing in <24 hours causing cerebral edema
- Seizures, coma, and respiratory arrests sometimes with little warning
- Neurogenic pulmonary edema (hypoxia may increase severity of brain swelling)
- Risk of herniation (particularly in young women and children)

Causes of Acute Hyponatremia With Fatal Cerebral Edema
- Self-induced water intoxication
  - Psychotic patients
  - Ecstasy (N-Methyl-3,4-methylenedioxyamphetamine)
  - Marathon runners
  - Radio contestants
- Post-operative iatrogenic hyponatremia
- Hyponatremia with intracranial pathology
Treating Acute Hyponatremia

How much correction of hyponatremia is "enough" to prevent complications in severe acute hyponatremia?

First Successful Rx

- 64 yr old woman post hysterectomy given 8 liters water by proctoclysis
- 36 hrs post op: seizures, coma, cyanosis, opisthotonos, Cheynes-Stokes respirations, bilateral Babinski signs
- Rx: 130 ml bolus infusion of 5% saline (equivalent to 217 ml of 3% saline)

Helwig FC, JAMA 1938;110:644–645

Infusion of 100 to 300 ml of hypertonic saline recommended for the rare patient with severe symptoms of water intoxication


Consensus Conference on Rx of Acute Hyponatremia in Marathon Runners

Recommended Therapy:
- In the field: 3% saline 100 ml over 10 minutes, repeated x 2 if needed
- In hospital: 3% saline 100 ml or 1 ml/kg bolus followed by 100 ml/hr or 1-2 ml/kg/hr


Therapeutic Hypernatremia for Cerebral Edema

- 30 ml bolus of 23.4% saline (equivalent to 234 ml 3% saline)
- △ Serum Na = 5 mEq/L
- Reversed clinical signs of brain herniation in most cases
- Decreased intracranial pressure by 40%

Koenig, MA. Neurology 70: 1023;1029, 2008

Brain Volume & Intracranial Pressure

Hypertonic Saline for Seizures, Coma or Cerebral Edema: Data @ ≤ 4 hours

Sterns, Semin Nephrol 29:282-299, 2009

4 to 6 mEq/L Increase Appears To Be Enough

Pitfalls in Correcting Acute Hyponatremia

- Delayed absorption of ingested water
  - Spontaneous decrease in serum Na after admission in runners and users of ecstasy
- Desalination of infused saline
  - Natriuresis in SIADH

"Desalination" in SIADH

22 Women After Routine Hysterectomy


Desalination & Hyponatremia

Vasopressin  Hypertonic Urine
  plus
Large Isotonic or Hypotonic Intake

Hyponatremia

"Desalination" of 0.9% NaCl

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
<th>Net</th>
</tr>
</thead>
<tbody>
<tr>
<td>154 mEq</td>
<td>154 mEq</td>
<td>308 mEq</td>
</tr>
<tr>
<td>2 liters</td>
<td>1 liter</td>
<td>+1 liter</td>
</tr>
</tbody>
</table>
Vaptans for Acute Hyponatremia?

- 66.7% of patients had increase ≥ 4 mmol/l in 24 hours
- 44.4% of patients increased by ≥ 4 mmol/l within 6 hours


Case Three

A Patient with DI and Hyponatremia

A 30-yr-old White man with Langerhans cell histiocytosis complicated by complete neurogenic DI is admitted for pneumonia.

DDAVP (desmopressin) the medication he normally takes to control his DI is continued.

On admission, his serum sodium concentration is 132 mEq/L.

Rx: DDAVP subcut q12 h and D5 ½ NS

Three days after admission his serum sodium concentration is found to be 105 mEq/L.

He complains of nausea and difficulty concentrating, but he is otherwise asymptomatic.

IV fluids are stopped and fluid intake is restricted.

A Patient with DI and Hyponatremia

Which ONE of the following would be the most appropriate management now?

A. Stop DDAVP for 24 hours
B. Stop DDAVP for 24 hours + 3% NaCl @ 25 ml/hr
C. Continue DDAVP + Conivaptan
D. Continue DDAVP + 0.9% NaCl @ 200 ml/hr
E. Continue DDAVP + 3% NaCl @ 25 ml/hr

Goals of the Case

- To recognize patients at risk of complications from rapid correction of hyponatremia
A Patient with DI and Hyponatremia

Which ONE of the following would be the most appropriate management now?

A. Stop DDAVP for 24 hours
B. Stop DDAVP for 24 hours + 3% NaCl @ 25 ml/hr
C. Continue DDAVP + Conivaptan
D. Continue DDAVP + 0.9% NaCl @ 200 ml/hr
E. Continue DDAVP + 3% NaCl @ 25 ml/hr

Chronic Hyponatremia

- Hyponatremia developing in >48 hours
  - Known duration >48 hrs (grey zone 24-48 hrs)
  - Presumed in patients drinking conventional amounts of water at home
- Minimal brain swelling & no risk of herniation
- Reversible neurological symptoms
- Risk of osmotic demyelination syndrome after rapid correction

Brain Response to Hyponatremia

- Brain Cell Osmolality = Plasma Osmolality
- Brain Cell Osmolality = Cell Solute/Cell Water

Early
- Solute/Water
- Normonatremia
- Solute/Water
- Hyponatremia

Late
- Solute/Water
- Normonatremia
- Solute/Water
- Hyponatremia

Organic Osmolytes

- Once called “idiogenic osmoles”
- Intracellular osmotically active organic solutes that can vary in concentration without perturbing cell function
- Brain osmolytes lost over 24 to 48 hours in response to hyponatremia

Brain Adaptations after Correction of Chronic Hyponatremia

- Sodium chloride expands the interstitial space – minutes
- Recovery of potassium – hours
- Recovery of organic osmolytes – up to 5 days
Osmotic Demyelination Syndrome

- Delayed post-therapeutic neurological deterioration developing one to several days after rapid correction of chronic hyponatremia
- Patients get neurologically worse after their electrolytes get better


Osmotic Demyelination: Human Disease Reproduce in Animals


A Patient with DI and Hyponatremia

Which ONE of the following would be the most appropriate management now?

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D. Continue DDAVP + 0.9% NaCl @ 200 ml/hr
E. Continue DDAVP + 3% NaCl @ 25 ml/hr

Experimental model for ODS in the rat:

- 3 days hyponatremia induced with DDAVP + H2O
- Stop DDAVP
- Serum Na rapidly returns to normal
- Maximally dilute urine = >500 ml/hr = >2 mEq/L/hr
- In DI, hypernatremia if patient unable to seek water

C. Continue DDAVP + Conivaptan
   - No data on effectiveness of vaptan in patient receiving DDAVP
D. Continue DDAVP + 0.9% NaCl @ 200 ml/hr
   - DDAVP = SIADH
   - SIADH + NS = Desalination and hyponatremia
Case Four

A beer drinker with profound hyponatremia

A 45 year old beer drinker (approximately 20 cans of beer daily) was found unresponsive in his apartment. On arrival, he was combative and disoriented requiring sedation.

PMH:
Frequent admissions for alcohol withdrawal seizures and delirium tremens.

PMH:
Three years prior to this admission: presented with a serum sodium concentration of 115 mEq/L (his only prior episode of hyponatremia) shortly after beginning an SSRI. During treatment his urine osmolality had fallen to 70 mOsm/kg with a urine output of 3150 ml over 5 hours

Two weeks prior to admission:
He was normonatremic when hospitalized for a withdrawal seizure. After discharge he was started on a thiazide diuretic for hypertension and an SSRI for depression

Laboratory Data on Admission
- Serum Na 96, K 2.4, Cl 56, HCO3 26 mmol/l
- BUN 9, Creatinine 1.0, Glucose 119 mg/dl
- Plasma osmolality 203 mOsm/kg, undetectable blood alcohol
- Urine osmolality 732, Urine Na 7 mEq/L

Laboratory Data on Admission (cont)
- Albumin 4.2 gms/dl, Total bilirubin 2.5 mg/dl, AST 599 U/L, ALT 218 U/L
- Creatinine phosphokinase 19,785 U/L
A beer drinker with profound hyponatremia

- A CT scan of the head showed no cerebral edema, with images indistinguishable from a CT scan done three weeks earlier when the patient was normonatremic.

Chronic Hyponatremia

Serum Na 135 mEq/L, Serum Na 96 mEq/L

What are the best therapeutic targets to aim for over the next 6 and the next 24 hours:

<table>
<thead>
<tr>
<th>6 hour target</th>
<th>24 hour target</th>
</tr>
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<tbody>
<tr>
<td>A. 99 mEq/L</td>
<td>108 mEq/L</td>
</tr>
<tr>
<td>B. 102 mEq/L</td>
<td>102 mEq/L</td>
</tr>
<tr>
<td>C. 102 mEq/L</td>
<td>120 mEq/L</td>
</tr>
</tbody>
</table>

Goals

- To develop a strategy to avoid complications
  - Untreated hyponatremia
  - Excessively corrected hyponatremia

Serum Na <105 mEq/L

Rate of Correction and Outcome

Data from Sterns, Cappuccio, Silver JASN 1994;4:1322

Chronic Hyponatremia

- Duration known to be <48 hours (uncommon)
- Hyponatremia developing outside the hospital in a patient drinking conventional volumes of water
  - Not psychotic polydipsia
  - Not marathon runner
  - Not at a rave party
**Risk Factors for ODS**

- Chronic hyponatremia
- Serum Na < 105 mEq/L
- Hypokalemia
- Alcoholism and malnutrition
- Liver disease (case reports of CPM with correction < 10 mEq/L per 24 hours)

**Therapeutic Goals**

- 6 mEq/L is "enough" for the most severe symptoms
- How much is "too much"
  - 10 mEq/L/day in high risk groups
  - 18 mEq/L/2days
- How much is "just right"
  - Not too little and not too much
  - Enough margin for error
  - SUGGESTION: 6 mEq/L/day

**A beer drinker with profound hyponatremia (96 mEq/L)**

What are the best therapeutic targets to aim for over the next 6 and the next 24 hours:

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<tr>
<td>C. 102 mEq/L</td>
<td>120 mEq/L</td>
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</tbody>
</table>

**Correction Goals for Profound Hyponatremia**

**Rule of 6’s:**
- Six-a-day makes sense for safety
- Six in six hours for severe sx’s and stop

*For all patients with chronic hyponatremia the goal is 6 mEq/L over the initial 24 hours. For those with severe symptoms (seizure, severe delirium, unresponsiveness) the goal is preloaded in the first six hours, postponing subsequent efforts to raise the serum sodium to the next day.*


**A beer drinker with profound hyponatremia (96 mEq/L)**

Which Rx would best avoid seizures from hyponatremia & ODS from overcorrection

A. Conivaptan
B. Isotonic saline
C. 3% saline
D. Isotonic saline combined with desmopressin
E. 3% saline combined with desmopressin
**Unintended Overcorrection of Severe Hyponatremia**

- Without a non-osmotic stimulus, ADH is undetectable.
- Without ADH, urine is maximally dilute (<100 mOsm/kg).
- Maximally dilute urine = >500 ml/hr.
- >500 ml/hr urine output increases the sNa by > 2 mEq/L/hr.

**Pathogenesis of Hyponatremia**

**Hypovolemia & Hyponatremia**

- Hypovolemia
- Hyponatremia
- Normal Saline
- ADH

**Correction of Hyponatremia**

- Hypovolemia
- Thiazide diuretics
- Drug-induced SIADH
- Stress-induced SIADH
- Hypoxia
- Cortisol deficiency
Re-Induction of Hyponatremia Prevents Myelinolysis in the Rat

<table>
<thead>
<tr>
<th></th>
<th>Rapid Correction</th>
<th>Rapid Correction Plus Re-Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNa Pre-Rx</td>
<td>108 ± 2 mmol/l</td>
<td>104 ± 2 mmol/l</td>
</tr>
<tr>
<td>ΔSNa at 12 hrs</td>
<td>--</td>
<td>29 ± 1 mmol/l</td>
</tr>
<tr>
<td>ΔSNa at 24 hrs</td>
<td>29 ± 1 mmol/l</td>
<td>14 ± 1 mmol/l</td>
</tr>
<tr>
<td>Sx’s Day 5</td>
<td>12/12</td>
<td>1/16</td>
</tr>
<tr>
<td>Deaths Day 10</td>
<td>12/12</td>
<td>1/16</td>
</tr>
</tbody>
</table>


Therapeutic Re-Lowering

Oya, S. et al. Neurology 2001;57:1931

DDAVP to prevent and reverse unintended overcorrection
- 20 patients given DDAVP during Rx of hyponatremia because of:
  - Excessive correction
  - Faster than expected correction
  - Recognition of a water diuresis
- 6 patients corrected by >12 mEq/L before DDAVP
  - 1/3 of patients with sNa<120 mEq/L had overcorrected
- 14 patients re-lowered by 2-9 mEq/L
  - Well tolerated


Avoiding Overcorrection


Correction Goals

Rule of Six’s (in mEq/L)
- For Safety: 6-a-day
- For Severe Sx’s: 6 in 6 hrs & STOP

Correcting Hyponatremia

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

Add to the Numerator
Subtract From the Denominator

Options:
1) Wait for water losses and replace them
2) Wait for water losses and stop them with DDAVP
3) Eliminate water losses with DDAVP

Unplanned Water Diuresis
A beer drinker with profound hyponatremia (96 mEq/L)

Which Rx would best avoid seizures from hyponatremia & ODS from overcorrection

A. Conivaptan
B. Isotonic saline
C. 3% saline
D. Isotonic saline combined with desmopressin
E. 3% saline combined with desmopressin

Vaptans for profound hyponatremia?

- Limited published experience in patients with serum Na <120 mEq
- Unknown if DDAVP will stop vaptan-induced water diuresis

Overcorrection From Vaptans

- 38 pts in single center
- 9 pts corrected by > 8 mEq/L in 24 hours
- All patients with serum Na < 120 mEq/L corrected by ≥ 12 mEq/L in 24 hours
- No sequelae observed after overcorrection

Tolvaptan-Induced ODS

Isotonic saline for profound hyponatremia?

- 1 Liter 0.9% NaCl ⇒ 1 mEq/L △ SNa
- Unpredictable onset of water diuresis in multi-factorial hyponatremia
  - SSRI
  - Thiazide
  - Alcohol withdrawal
  - Recent seizure
- Combining with DDAVP ⇒ Desalination
Hypertonic saline for profound hyponatremia

- Reliably increases serum Na
- Unpredictable onset of water diuresis as with isotonic saline
- Can be combined with DDAVP

\[
\Delta \text{Serum Na with 1 L infusate} = \frac{\text{Infusate Na} - \text{Na}_0}{\text{Total Body Water} + 1}
\]

Mohmand et al, CJASN 2:1110-1117, 2007

Overcorrection from 3% NaCl

Mohmand et al, CJASN 2:1110-1117, 2007
Re-Induction of Hyponatremia Prevents Myelinolysis in the Rat

<table>
<thead>
<tr>
<th>Rapid Correction</th>
<th>Rapid Correction Plus Re-Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNa Pre-Rx</td>
<td>104 ± 2 mmol/l</td>
</tr>
<tr>
<td>ΔSNa at 12 hrs</td>
<td>29 ± 1 mmol/l</td>
</tr>
<tr>
<td>ΔSNa at 24 hrs</td>
<td>14 ± 1 mmol/l</td>
</tr>
<tr>
<td>Sx’s Day 5</td>
<td>12/12</td>
</tr>
<tr>
<td>Deaths Day 10</td>
<td>12/12</td>
</tr>
</tbody>
</table>


Oya, S. et al. Neurology 2001;57:1931

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  - Well tolerated


Combined Rx with DDAVP & 3%NaCl

- DDAVP 2 mcg q 8h started before 3%NaCl creating iatrogenic SIADH in all
- 3%NaCl to achieve desired rate of increase
  - 100 ml bolus for severe symptoms
  - 0.3 ml/kg/hr average dose in most patients
- 400 mM KCl can substitute for 3% NaCl
- No cases of overcorrection in >25 patients with sNa <120 mEq/L


Combined DDAVP + 3% NaCl

- Water intake must be restricted
  - Avoid in psychotic patients with polydipsia
- Adjust 3% NaCl if KCl is given
  - 400 mM KCl or po KCl: equivalent to 3% NaCl
  - 100 mM KCl: no adjustment needed
- DDAVP will not prevent all water losses:
  - Urea diuresis
  - Glycosuria

In press
Case Five

A Patient With SAH and Hyponatremia

A 40 year-old woman was admitted with the worst headache of her life.
- Admission labs: Na 140 K 3.9 Cl 105 CO2 22 BUN 17 Creat 1.0, Hct 37
- CT scan: Subarachnoid hemorrhage

During the first six days of hospitalization, she is treated with nimodipine and intravenous 0.9% saline at 200 ml/hr. Gradually the serum sodium concentration falls to 125 mEq/L. BP is now 148/66. Weight 58 kg. She is asymptomatic except for a headache.

Laboratory data:
- Na 124, K 4.2, Cl 91, CO2 22, BUN 11, Creat 0.9, Hct 34.
- Serum osmolality 260 mOsm/kg
- Urine osmolality 800 mOsm/kg
- Urine Na 240 mEq/L, Urine K 20 mEq/L.
- Urine output 200 ml/hr

0.9% NaCl is increased to 500 ml/hr:

Predicted \( \Delta S_{Na} \) after 1 liter of NS =

\[
\frac{\text{Infusate Na} - \text{Serum Na}}{\text{Total Body Water} + 1} = \frac{154 - 124}{29 + 1} = 1 \text{ mEq/L}
\]

The actual \( \Delta S_{Na} \) after 0.9% NaCl @500 ml/hr will be:

A. About the same as the predicted \( \Delta S_{Na} \) (0.5 mEq/L/hr)
B. More than the predicted \( \Delta S_{Na} \) because volume expansion should cause a water diuresis
C. Less than the predicted \( \Delta S_{Na} \) because a portion of the infused sodium will be excreted in the urine
D. The \( S_{Na} \) will fall in response to this therapy
Goal of Case

- To understand the pathogenesis of hyponatremia in neurological disease
  - Cerebral salt wasting
  - SIADH
- To understand the limitations of predictive formulas in the treatment of hyponatremia

A Patient with SAH and Hyponatremia

If the patient is Rx'd with NS 500 ml/hr, how will the actual increase in serum sodium concentration compare to the increase predicted by the equation (0.5 mEq/L/hr)?

A. About the same as predicted
B. More than predicted because volume expansion should cause a water diuresis
C. Less than predicted because a portion of the infused sodium will be excreted in the urine
D. The serum sodium concentration is likely to fall in response to this therapy

Differential diagnosis

Hypotonic hyponatremia with high urine sodium concentration
- SIADH
- Diuretic-induced
- Addison disease
- Renal salt wasting
- Cerebral salt wasting

Is this sodium wasting?

- Cerebral salt wasting--
  - Primary natriuresis
  - Secondary release of vasopressin due to volume contraction
- SIADH
  - Primary release of vasopressin
  - Secondary natriuresis due to volume expansion

Cerebral Salt Wasting?

- Described before pathophysiology of SIADH was understood
- More recently adopted by neurosurgery based on ambiguous data:
  - Low plasma and blood volumes
  - Low CVP
  - High natriuretic peptides


Cerebral Salt Wasting vs SIADH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSW</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour fluid balance</td>
<td>Negative</td>
<td>Even or slightly positive</td>
</tr>
<tr>
<td>Urine sodium excretion</td>
<td>&lt;6 cm H₂O, &gt; 20 mEq/L</td>
<td>&gt; 6 cm H₂O, &gt;20 mEq/L</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Increased or no change</td>
<td>Decreased or no change</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Upadhyay UM. J Intensive Care Med. 2011 Feb 23
SIADH vs CSW

Common Features

- High urine sodium
- Vasopressin present despite hyponatremia
- Increased levels of natriuretic peptides
- Low renin and aldosterone levels
- Low uric acid


FE Urate and Salt Wasting


Supporting a Diagnosis of SIADH

- Hyponatremia after large volumes of isotonic saline to increase cerebral perfusion
- Increased weight: 56 → 58 kg
- Decreased Hct: 36 → 34
- High BP: 148/66
- CVP is a tarnished gold standard

Hyponatremia in SAH: Management Problems

- Volume expansion recommended but of unproven benefit
- SIADH + Volume expansion may cause “desalination” and hyponatremia
  (Diringer MN, Clin Neuropharmacol. 1995;18:114-26)

Hyponatremia in SAH

- 19 patients with SAH Rx’d with high volume isotonic saline
  - 6/19 patients developed hyponatremia
  - Increased ANF
  - Low renin and aldo levels
  - Plasma AVP not correlated with Posm

  Diringer, Ann Neurol 1992;31:543-50
0.9% NaCl in Hyponatremia

- Hypovolemia
  - Provokes a water diuresis
  - May increase sNa by >2 mEq/L/hr
- SIADH
  - Provokes a natriuresis in a concentrated urine
  - May decrease sNa
- CHF
  - Increases edema with little change in sNa

SIADH: Worse with 0.9% Saline

Subtract from Numerator
(More sodium excreted than infused)
Serum $[\text{Na}^+] = \frac{\text{Na}^+_{E} + \text{K}^+_{E}}{\text{Total Body Water}}$
Add to Denominator
(More volume infused than excreted)

A Patient with SAH and Hyponatremia

Because of concern that the patient is at high risk of brain damage from untreated hyponatremia (young woman + CNS pathology) 3% saline is given at 60 ml/hr. The dose is based on the following rule of thumb:

1 ml/kg of 3% saline = 1 mEq/L $\triangle$ sNa

A Patient with SAH and Hyponatremia

An infusion of 3% saline at 1 ml/kg body weight/hr in this patient is:
A. Too fast
B. Too slow
C. Just right

3% Saline Rule of Thumb

- 3% saline = 0.5 mEq/ml
- TBW = 0.5 L/kg body weight
- 1 ml/kg increases the serum sodium concentration by 1 mEq/L

3% Saline Rule of Thumb

- 3% saline = 0.5 mEq/ml
- TBW = 0.5 L/kg body weight
- 1 ml/kg increases the serum sodium concentration by 1 mEq/L

Assumes that all of the saline is retained; does not consider urine losses of electrolyte or water
A Patient with SAH and Hyponatremia

Laboratory data:
- Na 124, K 4.2, Cl 91, CO2 22, BUN 11, Creat 0.9, Hct 34.
- Serum osmolality 260 mOsm/kg
- Urine osmolality 800 mOsm/kg
- Urine Na 240 mEq/L, Urine K 20 mEq/L.
- Urine output 200 ml/hr

Urine Na & K Losses
- 260 mEq/L
- 0.2 L per hour
- 52 mEq/hr

3% NaCl @ 50 ml/hr x 1 hr

Sodium Balance
In: 25 mEq
Out: 52 mEq
Net: - 27 mEq

Water Balance
In: 50 ml
Out: 200 ml
Net: - 150 ml

3% Saline @ 50 ml/hr x 1 hr

Serum \([\text{Na}^+] = \frac{\text{Na}^+ + \text{K}^+}{\text{Total Body Water}}\)

Net: - 27 mEq
Subtract 0.15 L

3% Saline @ 50 ml/hr x 1 hr

Net: - 0.15 L

Net: - 27 mEq

3% Saline @ 50 ml/hr x 1 hr

124 mEq/L = \frac{(30 \times 124 \text{ mEq})}{30 \text{ L}}

124 mEq/L = \frac{30 \times 124 \text{ mEq}}{30 \text{ L}}

124 mEq/L = \frac{30 \times 124 \text{ mEq}}{30 \text{ L}}

Subtract 27 mEq
Subtract 0.15 L
3% Saline @ 50 ml/hr x 1 hr

Subtract 27 mEq

\[
30 \times 124 \text{ mEq} = 123.7 \text{ mEq/L}
\]

Subtract 0.15 L

Serum Sodium Falls by 0.3 mEq/L/hr

Therapeutic Option
3% Saline @ 150 ml/hr

Even if sodium losses continue, 3% saline @ 150 ml/hr will provide sodium more rapidly than it is lost and with an infusate that is more concentrated than the urine can be.

Bottom Line

- Patients with subarachnoid hemorrhage often excrete large volumes of concentrated urine because of therapeutic volume expansion + SIADH (plus cerebral salt wasting?)
- Treatment requires large volume of hypertonic saline (e.g. 1.5% saline to match or exceed urine output)

Case Six

A dialysis patient with hyponatremia

- A 41 y.o. year old 120 kg male with ESRD, on hemodialysis presents with 1 wk history of abdominal pain, including "new" pain in RUQ, shortness of breath, nausea & vomiting. His last hemodialysis was 6 days ago (two missed Rx's).

PMH:
- ESRD
  - Nephrolithiasis
  - Gastric bypass age 18
- Depression
  - Alcohol & cocaine abuse
  - Medical non-compliance
  - Frequent missed dialysis treatments
- Chronic pancreatitis
- Recurrent GI bleeding due to AVM’s
A dialysis patient with hyponatremia

**Physical Exam:**
- BP 156/79 HR 91 R 18 O2 sat 98% RA, Wt 100 kg
- Alert and oriented
- No rub or gallow
- Lungs clear
- Soft tender abdomen
- 3 + peripheral edema
- Unremarkable neurological exam

**Laboratory:**
- BUN 48 mg/dl
- Creat 15.7 mg/dl

EKG: Normal QRS, no peaking of T waves

**What is the best Rx:**
A. His usual dialysis treatment
B. 3 amps of NaHCO3 IV
C. Tolvaptan + Kayexalate
D. 3 hrs dialysis with reduced blood flow and low sodium dialysate

**Hyponatremia and Hemodialysis**

- Rapid fall in BUN promotes brain cell swelling (dialysis dysequilibrium)
- Urea speeds brain reuptake of lost organic osmolytes by unknown mechanisms
- In vitro protection against pro-apoptotic effect of hypertonic stress

Osmotic Demyelination & Uremia

- IV and oral Urea used commonly in Belgium to Rx hyponatremia.
- No reports of CPM after rapid correction with urea.

Decaux, JAMA 1982; 247:471-474

ODS and Uremia

- Exogenous urea protects rats against myelinolysis.
  Soupart, Clin Sci 1991;80:77
- Hyponatremic rats with azotemia tolerate rapid, large increases in serum sodium concentration that cause myelinolysis and an 80% mortality in non-azotemic animals.
  Soupart, Brain Res 2000;852:167

Enhanced brain reuptake of myoinositol in uremia


ODS after dialysis

- 52 year old man with CKD admitted with uremic symptoms
  - Serum Na 100 mEq/L, K 3.53 mEq/L
  - BUN 102 mg/dl, Creatinine 17 mg/dl
- Hemodialysis x 2.5 hrs with BFR 150 ml/min
  - Post dialysis SNa 121 mEqL (∆ 8 mEq/L/hr)
- Post-dialysis ODS
  - Beginning 1 day post-dialysis
  - Facial diplegia, dysarthria, dysphagia, tetraparesis X 3 mos
  - Able to walk after 7 mos, with persistent disability

Huang, W-Yi. Renal Failure 2007;29:635-638

ODS after hemodialysis

“Despite the apparent infrequency of ODS in the dialysis population, and despite animal models suggesting that this degree of caution may not be necessary, we agree that predialysis serum sodium levels should help guide dialysis prescriptions”


CVVHD for profound hyponatremia

Viktorsdottir, O. J Am Soc Nephrol 2006;17:219A
CVVHD for profound hyponatremia

Dialysate sodium adjusted daily 7 to 10 mEq/L higher than SNa

Viktorsdottir, O. J Am Soc Nephrol 2006;17:219A

Dialysis Rx in Severely Hyponatremic Patients with ESRD

- Lowest commercially available dialysate setting = 130 mEq/L
- Total equilibration at low BFR
- Infused Na = BFR x time (Dialysate Na – SNa)
- ΔSNa ≈ infused Na/TBW


A Dialysis patient with hyponatremia

Laboratory:

<table>
<thead>
<tr>
<th>Pre-Dialysis</th>
<th>Post-Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>113</td>
<td>6</td>
</tr>
<tr>
<td>81</td>
<td>14</td>
</tr>
</tbody>
</table>

BUN 48 mg/dl
Creat 15.7 mg/dl
EKG: Normal QRS, no peaking of T waves
Body Weight = 100 kg

Slow correction with HD

- Lowest dialysate [Na] = 130 mEq/L
- Blood flow rate 100 ml/min = 6 L/hr
- Assume complete equilibration between blood and dialysate

Na infusion = 6L/hr x 3 hrs (130 – PNa)
Na infusion = 18 Liters x 17 mEq/L = 306 mEq
Predicted ΔPNa = 306 mEq/50 L = 6 mEq/L

Three-hour Hemodialysis

<table>
<thead>
<tr>
<th>Pre-Dialysis</th>
<th>Post-Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>113</td>
</tr>
<tr>
<td>Potassium</td>
<td>6</td>
</tr>
<tr>
<td>Chloride</td>
<td>81</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>14</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>18</td>
</tr>
<tr>
<td>BUN</td>
<td>53</td>
</tr>
<tr>
<td>Creatinine</td>
<td>16.7</td>
</tr>
<tr>
<td>Glucose</td>
<td>85</td>
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</tbody>
</table>