HYPONATREMIA MANAGEMENT IN THE HOSPITALIZED PATIENT: DON’T DRINK THE WATER
HYPONATREMIA TAKE HOME MESSAGES

• HypoNa results from ADH-induced retention of ingested or infused water.

• Treatment should always respect the how long hypoNa took to develop and the pathophysiology of the disease(s).

• HypoNa is a bad actor, especially when associated with a chronic disease.
HYPONATREMIA (NOT SO) FUN FACTS

• Not as “asymptomatic” as you might think
  • Gait instability, falls and fractures for Na 124-130 mmol/L
    • Renneboog B. American Journal of Medicine 2006;119:71.

• Independent predictor of inpatient mortality
  • Reached significance at Na < 138 mmol/L
  • 27% of patients with CHF and 50% of patients with cirrhosis

• Financial impact for hospitals:
  • 8% increase in LOS and 9% increase in cost
  • Increased risk of death in hospital, 30 days and 1 year
  • Increased risk of 30-day readmission
    • Deitelzweig S. Hospital Practice 2013;41:89-95.
ADH: ANTIDIURETIC HORMONE

• ADH is secreted from the posterior pituitary gland in response to reductions in plasma volume and to increases in plasma osmolality:
  • Secretion in response to reduced plasma volume is activated by pressure receptors in the veins, atria and carotids.
  • Secretion in response to hyperosmolality is mediated by osmoreceptors in the hypothalamus.

• ADH increases the permeability to water in the collecting tubules.

• Result: A smaller volume of concentrated urine.
Renal physiology & diuretics

Proximal part
Thiazides

Distal part
Osmotic, K-sparing

Collecting duct and tubules
Osmotic

PCT
Osmotic

Creatinine, Antibiotics, Diuretics, Uric acid

DCT

NaCl
K
H2O
HCO3-
Glucose, AA

K
H
Urea

NaCl
Ca

"PTH"
"Aldosterone"

NaCl
25

NaCl
10

NaCl
2-5

H2O

"ADH"

Cortex

Medulla

25 NaCl
K
H2O

Desc. limb
Mg
Ca

Asc. limb
Mg
Ca

Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange

Loop of Henle
Loop diuretics
COMMON STIMULI FOR ADH RELEASE
ACUTE VS CHRONIC HYPONATREMIA

- **Acute**: HypoNa can kill you.
  - Exercise associated
  - MDMA (ecstasy)
  - Primary Polydipsia
  - Post operative
  - SAH

- **Chronic**: The underlying disease kills you.
  - CHF
  - Malignancy
  - Advanced COPD
  - Dementia
  - Liver Failure
    - MELD-Na
URINE OSMOLALITY

• Hyponatremia should cause marked suppression of ADH resulting in a maximally dilute urine (<100 mOsm/L).

• $\text{U}_{\text{osm}}$ can help:
  • Distinguish between impaired and normal water excretion.
  • Determine how avidly the kidneys are hanging on to water.

• Along with increased urine output, can herald the onset of auto-correction.
  • $\text{U}_{\text{osm}} < 200 \text{ mOsm/L}$
URINE SODIUM

• Most helpful to distinguish between effective volume depletion and euvoletic states (SIADH).

  • Decreased effective circulating volume: $\text{UNa} < 25 \text{ mmol/L}$ unless kidney is the site of Na loss (e.g. diuretic)
    • Due to RAAS activation

  • SIADH: $\text{UNa} > 40 \text{ mmol/L}$
CASE 1: 64 YO ALCOHOLIC WITH WEAKNESS FROM OUTSIDE HOSPITAL

- Poor po intake, diarrhea and ankle pain from a fall.
- Lucid with normal neurologic exam.
- Stigmata of CLD.
  - Na 104 mmol/L
  - Bili 16 mg/dL
  - INR 1.8
  - Creatinine 0.85 mg/dL
  - Maddrey’s score 53

- Started on HTS at 50 mL/hr and transferred.
  - Na 106 mmol/L on arrival
1. Assess fluid intake
   beer, otherwise poor po
2. Look in the mirror (meds)
   none
3. Look for causes of ADH release
   diarrhea, pain, hypovolemia
4. Volume status assessment
   hypovolemic
5. Laboratory evaluation (blood and urine)
   $S_{osm} \ 237 \ \text{mOsm/L}, \ U_{Na} < 20 \ \text{mmol/L}$
   $U_{osm} \ 410 \ \text{mOsm/L}$
The desired rate of correction depends upon:

- Severity of symptoms
- Risk of herniation
- Risk of ODS
  - Na < 120 mmol/L
  - Rapidly reversible ADH
  - Alcoholic, Liver dz, malnutrition

If you don’t know, GO SLOW!
ROCK MEETS HARD PLACE
BRAIN HERNIATION VS OSMOTIC DEMYELINATION
## Cerebral Edema vs OSM

<table>
<thead>
<tr>
<th>Cerebral Edema</th>
<th>Osmotic Demyelination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- headache</td>
<td>- dysarthria</td>
</tr>
<tr>
<td>- weakness</td>
<td>- dysphagia</td>
</tr>
<tr>
<td>- nausea/vomiting</td>
<td>- paraparesis</td>
</tr>
<tr>
<td>- confusion</td>
<td>- ataxia</td>
</tr>
<tr>
<td>- seizures</td>
<td>- confusion</td>
</tr>
<tr>
<td>- respiratory arrest</td>
<td>- obtundation</td>
</tr>
<tr>
<td>- herniation</td>
<td>- coma</td>
</tr>
<tr>
<td>- death</td>
<td>- locked in syndrome</td>
</tr>
</tbody>
</table>
Normal state. The extracellular fluid is in osmotic equilibrium with the intracellular fluid, including that of the brain cells, with no net movement of water across the plasma membrane.

Acute hyponatremia. If the extracellular fluid suddenly becomes hypotonic relative to the intracellular fluid, water is drawn into the cells by osmosis, potentially causing cerebral edema.

Adaptation. Over the ensuing few days, brain cells pump out osmoles, first potassium and sodium salts and then organic osmoles, establishing a new osmotic equilibrium across the plasma membrane and reducing the edema as water moves out of the cells.

Overly aggressive therapy with hypertonic saline after adaptation has occurred raises the serum sodium level to the point that the extracellular fluid is more concentrated than the intracellular fluid, drawing more water out of the brain cells and causing the syndrome of osmotic demyelination.
OSMOTIC DEMYELINATION SYNDROME (ODS)

- Results from over-rapid correction of hypoNa.
- Recapturing of osmolytes opens up channels in BBB for immune-competent proteins that attack myelin.
- Areas of the brain that are the slowest to recapture osmolytes are most susceptible to ODS.
  - ETOH, liver disease, malnutrition
CORRECTION OF CHRONIC HYPONATREMIA (GOAL VS LIMIT)

- **Goal** 6 mmol/L over 24 hours.

- **Limit** 8 mmol/L for each 24 hour period.

- 24 hour change is more important than hour to hour change.

- Remember “Six a day makes sense for safety.”
CLINICAL IMPRESSIONS OF OUR PATIENT IN CASE 1

- Acute on chronic liver failure
- **Chronic hyponatremia** caused by:
  - Low solute state and elevated ADH from dehydration, diarrhea and pain.
  - Higher risk for ODS than herniation.

- **Plan:**
  - STOP HTS infusion
  - prednisolone for acute liver failure (Maddrey’s > 32)
  - volume replacement with NS
  - treat pain and diarrhea
  - 1.25 L/day fluid restriction
HOSPITAL COURSE

<table>
<thead>
<tr>
<th></th>
<th>Na (mmol/L)</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hrs</td>
<td>104 → 110</td>
<td>1,760 mL</td>
</tr>
<tr>
<td>Next 16 hrs</td>
<td>110 → 121</td>
<td>3,150 mL</td>
</tr>
</tbody>
</table>

After first 24 hour period:
- Diarrhea and pain controlled.
- Eating regular diet.
- IVF stopped.

Why did urine output and Na increase by so much?
- We shut off his ADH leading to aquareasis
STRATEGIES TO AVOID OVER-RAPID CORRECTION

- Stop HTS infusion
- Liberalize fluid intake
- Desmopressin (DDAVP): 2 mcg IV (repeat doses Q6 hours as needed)
- D5W 3 mL/kg/hr
HOSPITAL COURSE AND SHORT TERM FOLLOW UP

• 2 mcg DDAVP and D5W infusion to slow rate of correction.
  • Na 121 → 120 → 116 → 117 mmol/L over next 8 hours.
• Clinical improvement.
• Na increased incrementally over next 4 days and stabilized at 131 mmol/L.

• Discharged to SNF for physical rehabilitation.
• 30-day alcohol rehabilitation.
• Na 135 mmol/L at 3 month clinic follow up.
RISK FACTORS FOR OSMOTIC DEMYELINATION SYNDROME (ODS)

- Na level on admission < 120 mmol/L
- Chronicity (> 48 hrs)
- Rate of correction > 12 mmol/L per day
- Patients more susceptible to ODS:
  - Alcoholics
  - Malnutrition
  - Liver disease
PATIENTS AT RISK FOR OVER-RAPID CORRECTION OF HYponatremia

1. Following therapy specifically directed at raising the Na such as HTS (hypertonic saline).

2. Following **cessation of a rapidly reversible stimulus for ADH** release.
   - Saline administration to patients with true volume depletion
   - Glucocorticoids to patients with adrenal insufficiency
   - Discontinuation of causative drugs
     - HCTZ, carbamazepine and SSRI’s
   - Spontaneous resolution of a transient cause of ADH
     - surgical stress, high emotion, pain, nausea, hypovolemia
CASE 2: 57 YO ALCOHOLIC PRESENTS FROM DETOX AFTER A FALL

- Poor po intake, weakness.
- Benign exam, oriented x 3.
- Hypovolemic hyponatremia at 118 mmol/L.
- Started on NS at 150 mL/hr.

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>Na (mmol/L)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/4: 7:50 PM</td>
<td>118</td>
<td>FENa &lt; 1, UNa 11</td>
</tr>
<tr>
<td>4/4: 11:37 PM</td>
<td>127</td>
<td>Uosm 110 mOsm/L</td>
</tr>
<tr>
<td>4/5: 2:55 AM</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>4/5: 7:58 AM</td>
<td>132</td>
<td>Hospitalist switch</td>
</tr>
<tr>
<td>4/5: 10:00 AM</td>
<td>133</td>
<td></td>
</tr>
</tbody>
</table>
HOSPITAL COURSE(S) AND SHORT TERM FOLLOW UP

• Discharged home 4/9/16.

• Readmitted 4/11/16 - 4/14/16 with ataxia. CT head negative. Discharged to TCU.

• Readmitted 4/27/16 - 5/2/16 with confusion and ataxia. MRI showed ODS. Discharged to TCU.

• Clinic follow up 8/3/16: MOCA 17/30 and still ataxic.
PEARLS FOR CASES 1 AND 2
(OSMOTIC DEMYELINATION SYNDROME)

• Be aware of risk factors for ODS and susceptible patients.

• Be aware of cases with quickly reversible stimuli for ADH release.
  • watch urine output and urine osmolality

• If you don’t know, GO SLOW!
CASE 3: EXERCISE ASSOCIATED HYponatREMIA (EAH): A CAUTIONARY TALE

- A healthy physician decides to ride his bike 56 miles on his 56th birthday on a 95 degree August day.

- Trip highlights:
  - At mile 31 he vomited.
  - At mile 39 he developed severe leg cramps.
  - At mile 51 headache.

- On the way to the hospital, he had a GTC seizure.

- In the Emergency Department:
  - Altered
  - Had another GTC seizure
  - Na 106 mmol/L
ROCK MEETS HARD PLACE
BRAIN HERNIATION VS OSMOTIC DEMYELINATION
**CASE 4: MANAGEMENT OPTIONS**

(MOST APPROPRIATE **FIRST** STEP)

1. 100 mL of HTS over 10 minutes.
2. Normal saline infusion at 150 mL/hr.
3. Go grab a latte because you have plenty of time.
4. HTS infusion at 30 mL/hr.
CASE 4: MANAGEMENT OPTIONS
(HOSPITAL COURSE)

1. 100 mL of HTS over 10 minutes.

2. Normal saline infusion at 150 mL/hr.

3. Go grab a latte because you have plenty of time.

4. HTS infusion at 30 mL/hr.

- 100 mL of HTS over 10 minutes followed by 20 mL/hour.

- Repeat Na 110 mmol/L, thus HTS stopped.

- Brisk aquareasis and auto-correction over next 48 hours.
EAH: A CAUTIONARY TALE

• Hyponatremia caused by the “perfect storm”:
  • Insensible Na loss
  • High emotion
  • Vomiting
  • Pain
  • Excessive water intake
  • High ADH levels

• “Hyperacute” hyponatremia
  • No reported cases of ODS in EAH

• Tom: “why?”
  • “because I’m an idiot.”
HTS (3% SALINE) FOR ACUTE SEVERE AND SYMPTOMATIC HYponatremia

- 0.9% saline contains 308 mOsm/L NaCl
- 3.0% saline contains 1026 mOsm/L NaCl
- 2.0% saline contains 684 mOsm/L NaCl

Correction of Hyponatremia:
Goal 4-6 mmol/L RAPIDLY over several hours
Limit 8 mmol/L at 24 hours and 16 mmol/L at 48 hours*
(*unless hyperacute hyponatremia)

3% SALINE EMERGENCY THERAPY
“HOT SALT”

• 100 mL bolus will raise Na 2-3 mmol/L which decreases cerebral edema.

• Acute hyponatremia with severe symptoms.

• Goal is to RAPIDLY increase the Na by 4-6 mmol/L over several hours.
FATAL HERNIATION

• Happens almost exclusively in the following groups:
  • \textit{Post-op hypothyroid (women > men)}

• \textit{Massive water ingestion} associated with:
  • Psychosis
  • Extreme exercise
  • Ecstasy (MDMA)
  • Stupid contests

• \textit{Intracranial pathology (SAH)}
**Normal state.** The extracellular fluid is in osmotic equilibrium with the intracellular fluid, including that of the brain cells, with no net movement of water across the plasma membrane.

**Acute hyponatremia.** If the extracellular fluid suddenly becomes hypotonic relative to the intracellular fluid, water is drawn into the cells by osmosis, potentially causing cerebral edema.

**Adaptation.** Over the ensuing few days, brain cells pump out osmoles, first potassium and sodium salts and then organic osmoles, establishing a new osmotic equilibrium across the plasma membrane and reducing the edema as water moves out of the cells.

**Overly aggressive therapy** with hypertonic saline after adaptation has occurred raises the serum sodium level to the point that the extracellular fluid is more concentrated than the intracellular fluid, drawing more water out of the brain cells and causing the syndrome of osmotic demyelination.
EXERCISE ASSOCIATED HYPONATREMIA (EAH) IN MARATHON RUNNERS

- Boston marathon:
  - 30,000 runners
  - 992 portable toilets
  - 28,200 bananas
  - 35,000 gallons of water

- 488 runners (healthy volunteers)
  - 13% < 135 mmol/L
  - 0.6% < 120 mmol/L

“Perfect storm” of:
- Insensible Na loss from excessive sweating
- Excessive water intake
- Physiologic ADH release
- Pathologic ADH: pain, nausea, emotion
JUST (DON’T) DO IT!

Pain
Sweat
Cool medal
Water

Rob
SPORTS DRINKS: THINGS AREN’T ALWAYS AS THEY SEEM

• Do not provide significantly better protection against hyponatremia when compared with water.

• One famous sports drink has a Na\(^+\) plus K\(^+\) concentration of 23 mOsm/L compared with 145 mOsm/L in normal plasma.
PEARLS FOR CASE 3
(ACUTE MANAGEMENT OF EAH)

• 100 mL bolus of HTS is safe and effective.

• Large output of dilute urine heralds corrective aquareesis.

• Don’t run marathons!
  • Let thirst guide the way.
HYPONATREMIA TAKE HOME MESSAGES

• HypoNa results from ADH-induced retention of ingested or infused water.

• Treatment should always respect the how long hypoNa took to develop and the pathophysiology of the disease(s).

• HypoNa is a bad actor, especially when associated with a chronic disease.