A Balancing Act: Management of Euvolemic Hyponatremia

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Disclosures

• Nothing to disclose

Objectives

• Explain the regulatory pathways involved with sodium and water homeostasis
• Assess a patient to determine the etiology of hyponatremia
• Recommend a treatment plan for a patient with syndrome of inappropriate antidiuretic hormone (SIADH)
• Evaluate appropriateness of “vaptans” in treatment of euvolemic hyponatremia

Hyponatremia

• Sodium (Na) less than 135 mEq/L
• Most common electrolyte abnormality
• Disorder of water balance
• A clinical feature in 15–20% of emergency admissions to hospital
• Associated with increased mortality, morbidity, length of hospital stay, and increased hospital costs
• Prevalence
• Increasing with age
• Higher among women
• Independent predictor of mortality
• Guidelines
• European Journal of Endocrinology. 2014; 170: G1–G47.
• Am J Med. 2013; 126: S1–S42.

Symptoms by Classification

<table>
<thead>
<tr>
<th>Mild Na 130–134 mEq/L</th>
<th>Moderate Na 125–129 mEq/L</th>
<th>Severe Na &lt; 125 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Malaise</td>
<td>Headache</td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Vomiting</td>
<td>Confusion</td>
</tr>
<tr>
<td>Impaired attention</td>
<td>Confusion</td>
<td>Seizure</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Anorexia</td>
<td>Coma</td>
</tr>
<tr>
<td>Gait abnormalities</td>
<td>Unsteadiness</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td>Falls</td>
<td>Muscle cramps</td>
<td>Death</td>
</tr>
</tbody>
</table>

Sodium and Water Homeostasis

Osmotic – Vasopressin/Antidiuretic Hormone (ADH)

• Secreted by posterior pituitary when plasma osmolality increases by >2%
• Works at collecting tubule
• Binds to V2 receptors
• Creates aquaporin channels
• Water reabsorption
• Increases thirst

Non-Osmotic – Aldosterone

• Decreased circulating volume and decreased blood pressure activates arterial baroreceptors
• Stimulates RAAS system → ADH and aldosterone release
• Aldosterone
• Secreted from adrenal cortex
• Increase sodium and water reabsorption at distal convoluted tubule
Sodium and Water Homeostasis

Homeostasis (normal extracellular fluid volume)

Decreased water intake, increased urinary water loss, increased urinary Na⁺ loss

Increased blood volume and atrial distension (fluid gain or Na⁺ and fluid gain)

Decreased aldosterone release, decreased ADH release, decreased thirst

Increased natriuretic peptide release

Increased aldosterone and ADH release

Increased thirst → increased water intake; decreased urinary water loss; increased urinary Na⁺ retention

Increased renin secretion and angiotensin II activation

Decreased blood volume and blood pressure (fluid loss or fluid and Na⁺ loss)

Increased renin secretion and angiotensin II activation

Increased aldosterone and ADH release

Increased thirst

Decreased aldosterone release, increased ADH release, decreased thirst

Decreased blood volume and blood pressure (fluid loss or fluid and Na⁺ loss)

Increased thirst

Decreased aldosterone release, decreased ADH release, decreased thirst

Decreased blood volume and blood pressure (fluid loss or fluid and Na⁺ loss)

Increased thirst

Decreased aldosterone release, decreased ADH release, decreased thirst

Audience Participation #1

• MS is a 47 y/o female presenting to the medicine service
• Chief complaint: weakness secondary to stomach flu + can’t keep down fluids x2 days
• PMH: HTN
• Home meds: Amlodipine 5 mg daily

Which of the following options represent how her body would attempt to self regulate?

• A) Decreased aldosterone release, decrease ADH release, decreased thirst
• B) Increased aldosterone release, increase ADH release, increased thirst
• C) Increased aldosterone release, decrease ADH release, increased thirst
• D) Decreased aldosterone release, increased ADH release, decreased thirst

Drug Induced Hyponatremia

• TCAs, SSRIs, MAOIs, antipsychotics, anti-epileptics, antineoplastic agents, opiates
• Thiazide diuretics, amiloride, loop diuretics
• Anti-diabetic drugs, anti-epileptics, IV cyclophosphamide, NSAIDS

Evaluation of Hyponatremia

Serum Osmolality

Isotonic hyponatremia

Hypertonic hyponatremia

Hypotonic hyponatremia

Hypovolemic

Hypervolemic

Euvolemic

Renal losses and extrarenal losses

Heart failure, cirrhosis, nephrotic syndrome

Hypothyroid, hypokalaemia, SIADH, low solute intake

Presentation of Hyponatremia

• Urine osmolality > 450 mOsm/kg
• Urine Na⁺ > 20 mEq/L for renal losses
• Urine Na⁺ < 20 mEq/L for non-renal losses

• Urine osmolality > 100 mOsm/kg
• Urine Na⁺ > 20 mEq/L

• Urine osmolality > 100 mOsm/kg
• Urine Na⁺ > 20 mEq/L
Acute vs Chronic Hyponatremia

**Acute**
- > 48 hours
- Brain edema
- Glutamate deficiency
- Impaired norepinephrine function

**Chronic**
- < 48 hours
- No brain edema

Complications of Treatment

- Cerebral edema
- Osmotic demyelination syndrome

Correcting Acute Hyponatremia

- **Indications**
  - Self induced water intoxication
  - Known duration of hyponatremia 24-48 hours
  - Intracranial pathology or increased intracranial pressure
  - Seizures or coma regardless of known chronicity
- **Goal**
  - Urgent correction by 4-6 mEq/L to prevent brain herniation and neurological damage from cerebral ischemia
- **Treatment Recommendations**
  - Severe symptoms: 100 mL 3% NaCl IV over 10 minutes x3 PRN
  - Mild to moderate symptoms: 3% NaCl IV at 0.5-2 mL/kg/hr

Correcting Chronic Hyponatremia

- **Controversial rates of correction**
  - 4-6 mEq/L per day
  - Up to 12 mEq/L per day
- **High risk of Osmotic Demyelination Syndrome**
  - Na ≤ 105 mEq/L
  - Hypokalemia
  - Alcoholism
  - Malnutrition
  - Advanced liver disease
- **Excessive Correction**
  - Desmopressin
  - Free water

Hyponatremia Treatment Equations

- Estimating effect of 1 liter of any infusate on serum Na+
  \[ \Delta [Na+]_{serum} = (Na^+_{infusate} - Na^+_{serum})/(Total \ Body \ Water + 1) \]
- Estimating extra cellular fluid (ECF) volume deficit
  \[ ECF_{Vd} = ECF_{V_{norm}} - ECF_{V_{current}} \]

<table>
<thead>
<tr>
<th>Infusate</th>
<th>Infusate Na+</th>
<th>ECF Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% NaCl</td>
<td>133 mEq/L</td>
<td>100%</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>154 mEq/L</td>
<td>100%</td>
</tr>
<tr>
<td>Lactated Ringer's</td>
<td>130 mEq/L</td>
<td>97%</td>
</tr>
<tr>
<td>0.45% NaCl</td>
<td>77 mEq/L</td>
<td>73%</td>
</tr>
<tr>
<td>D5W</td>
<td>0 mEq/L</td>
<td>40%</td>
</tr>
</tbody>
</table>

* Complete distribution into ECF = induces osmotic removal of water from intracellular compartment

Population | Total body water
---|----------------
Children/Men < 70 years old | 0.6 x body weight (kg)
Men ≥ 70 years old | 0.5 x body weight (kg)
Women ≥ 70 years old | 0.45 x body weight (kg)

Audience Participation #2

- **MP is a 58 y/o CM, PMH significant for HTN, DM, hypothyroidism, COPD**
- **Social History:** 3-4 drinks/week, 60 pack-year smoking history (quit 6 months ago)
- **Home Medications:**
  - Glipizide 5 mg PO BID
  - Levothyroxine 0.075 mg PO daily
  - Lisinopril 20 mg PO daily
  - Metformin 1000 mg PO BID
  - Tiotropium 18 mcg inhaled daily
  - Albuterol inhaler 1 puff q6h prn shortness of breath
- **Presentation:**
  - 3 day history of headache, lethargy, and confusion
  - 3 month history of hemoptysis, shortness of breath, and worsened chronic cough
Audience Participation #2

- Relevant labs upon complete work-up:
  - Na – 118 mEq/L
  - TSH – WNL
  - Cortisol - WNL
  - Scr – 0.89 mg/dL
  - Urine Osmolality: 653 mOsm/kg  Urine Na: 78 mEq/L
- Relevant imaging:
  - CX-Ray reveals – left upper lobe nodule
- Relevant physical exam findings
  - Euvolemic

Syndrome of Inappropriate Antidiuretic Hormone

- Most common cause of euvolemic hyponatremia
- First described in bronchogenic carcinoma
  - Lack of of physiologic stimulus for release of antidiuretic hormone
- Antidiuretic hormone later found to be arginine vasopressin
- Not all patients with SIADH have elevated circulating levels of arginine vasopressin so the term SIAD was proposed
- Increased prevalence with increasing age
  - Prevalence especially high amongst nursing home patients

Causes of SIADH

- Malignancy
- Pulmonary Disease
- CNS Disorders
- Drugs
- Transient Causes

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Pulmonary Disease</th>
<th>CNS Disorders</th>
<th>Drugs</th>
<th>Transient Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Pneumonia</td>
<td>Infection</td>
<td>SSRIs</td>
<td>Endurance exercise</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Asthma</td>
<td>Subdural hematoma</td>
<td>TCAs</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>GI</td>
<td>Cystic fibrosis</td>
<td>SAH</td>
<td>Carbamazepine</td>
<td>Nausea</td>
</tr>
<tr>
<td>GU</td>
<td>Tuberous sclerosis</td>
<td>CVA</td>
<td>Nicotine</td>
<td>Pain</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>Aspergillosis</td>
<td>Brain tumors</td>
<td>Narcotics</td>
<td>Stress</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>Resp. failure associated with positive pressure breathing</td>
<td>Delirium tremens</td>
<td>AVP analogues (desmopressin, oxytocin, vasopressin)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Criteria for SIADH

- Serum osmolality <275 mOsm/kg
- Urine osmolality >100 mOsm/kg
- Clinical euvelmia
- Urine sodium > 30 mEq/L
- Absence of adrenal, thyroid, pituitary, or renal insufficiency
- No recent diuretic use

Treatment of SIADH

- Fluid restriction
  - Ideal for mild to moderate SIADH
  - Treatment of choice despite suboptimal evidence
  - Restrict all fluids – not just water
  - Aim for fluid restriction ~500 mL/day below 24 hour urine volume
- Complications of fluid restriction
  - Difficult adherence
  - Significant change takes time
  - Predictors of unsuccessful fluid restriction
    - Urine osmolality > 500 mOsm/kg
    - Urine Na⁺ < Urine K⁺ > serum Na⁺
  - 24 hour urine volume < 1500 mL/day
  - Increase in serum Na⁺ < 2 mEq/L/day in 24-48 hours on fluid restriction < 1 L/day

Treatment of SIADH

- Hypertonic saline (3% NaCl)
- Treatment of choice for acute symptomatic SIADH
- Demeclocycline
  - Induces nephrogenic diabetes insipidus
  - Decreases urine concentration despite elevated AVP
  - 600-1200 mg/day in divided doses – titrate every 3-4 days
- Adverse effects
  - Reversible azotemia/renal toxicity
  - Rash
- Urea
  - Increases solute free water excretion/decreases urinary Na+ excretion
  - 15-60 g/day – titrate weekly
  - Dissolve in strongly flavored beverage
- Not available in convenient FDA approved form

Vasopressin Receptor Antagonists

<table>
<thead>
<tr>
<th>Conivaptan (Vaprisol®)</th>
<th>Tolvaptan (Samsca®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td>V₁ and V₂</td>
</tr>
<tr>
<td>Initial Dosing</td>
<td>20 mg IV x1 over 30 minutes</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>20-40 mg IV over 24 hours – may administer for 1-4 days</td>
</tr>
<tr>
<td>Onset of action</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>5 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic: extensive via CYP3A</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Infusion site reaction, pyrexia, hypokalemia, headache, orthostasis</td>
</tr>
<tr>
<td></td>
<td>Thirst, dry mouth, asthenia, constipation, polyuria, hyperglycemia</td>
</tr>
<tr>
<td>Estimated Cost (average AWP)</td>
<td>$744/20 mg</td>
</tr>
<tr>
<td></td>
<td>$429/15 mg</td>
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</tbody>
</table>

Audience Participation #3

- EM is a 68 y/o male with PMH significant for CAD, HTN, and a fairly new diagnosis of depression. He presents to the internal medicine service after a fall at home. He has also been experiencing some mild confusion, nausea, and general malaise. His daughter is concerned that the citalopram is causing these symptoms.

- Home medications:
  - Aspirin 81 mg PO daily
  - Atorvastatin 80 mg PO daily
  - Citalopram 10 mg PO daily (started ~1 month prior to admission)
  - Ibuprofen 400 mg PO 2 pd pm pain
  - Lisinopril 10 mg PO daily
  - Metoprolol 25 mg PO BID

- Relevant labs upon complete work-up:
  - Na – 125 mEq/L
  - TSH – WNL
  - Cortisol - WNL
  - SCr – 0.67 mg/dL
  - Urine Osmolality: 523 mOsm/kg Urine Na: 64 mEq/L
  - Relevant imaging
    - Left hip – no signs of fracture
  - Relevant physical exam findings
    - Euvolemic
    - Social
      - No drugs, alcohol, lives at home with his wife, completes AED independently

- EM is diagnosed with SIADH based on diagnosis of exclusion. Which of the following represent the most ideal initial treatment plan for him?
  - A) stop citalopram, institute fluid restriction
  - B) stop citalopram, start sertraline
  - C) stop citalopram, start urea
  - D) stop citalopram, start tolvaptan

- Relevant labs upon complete work-up:
  - Na – 125 mEq/L
  - TSH – WNL
  - Cortisol - WNL
  - SCr – 0.67 mg/dL
  - Urine Osmolality: 523 mOsm/kg Urine Na: 64 mEq/L
  - Relevant imaging
    - Left hip – no signs of fracture
  - Relevant physical exam findings
    - Euvolemic
    - Social
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  - C) stop citalopram, start urea
  - D) stop citalopram, start tolvaptan
SALT Trials (SALT-1 and SALT-2)

**Study Design**
- Two, multi-center, randomized, double-blind, placebo controlled trials
- Tolvaptan vs placebo on treatment of hypervolemic and euvolesmic hyponatremia of diverse causes

**Primary Endpoints**
- Change in the average daily area under the curve (AUC) for the serum sodium concentration from baseline to day 4 and from baseline to day 30

**Select Secondary Endpoints**
- Change in AUC for serum sodium concentration, absolute serum sodium at each visit, time to sodium normalization, % of patients with normal sodium concentrations at days 4 and 30

**Inclusion Criteria**
- Age >18 y/o and Na < 135 mEq/L
- Euvolemic or hypervolemic hyponatremia (HF, cirrhosis, SIADH)
- At least 50% of enrolled subjects had to have Na < 130 mEq/L

**Select Exclusion Criteria**
- Psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency
- Recent cardiac surgery, myocardial infarction, sustained ventricular tachycardia
- SBP < 90 mm Hg; SCr > 3.5 mg/dL; Child Pugh score > 10; Na < 120 mEq/L; UTI; pulmonary hypertension; uncontrolled DM

**Intervention**
- Tolvaptan 15 mg PO daily
- Increase by 15 mg increments daily during first 4 days up to 60 mg daily

**Endpoints**
- Change in the average daily area under the curve for serum sodium concentration, % of patients with normal sodium concentrations at each visit, time to sodium normalization, % of patients with normal sodium concentrations at days 4 and 30

**Results**
- Sodium increased more in tolvaptan group than placebo group
  - Day 4 (p<0.001) – average increase 3.6 mEq/L
  - Day 30 (p<0.001) – average increase 4.5 mEq/L
- No difference in number patients requiring fluid restriction
- Adverse effects – constipation, thirst, dry mouth, increased urination
- 4 patients in tolvaptan group had rise of sodium exceeding desired threshold (>0.5 mEq/L/hr)

**Limitations**
- Majority of patients studied sodium 130-134 mEq/L
- No difference in number patients requiring fluid restriction
- After 7 day follow-up sodium had returned to baseline

**Additional Vaptan Studies**

**SALTWATER**
- Assessed long term safety and efficacy of tolvaptan for treatment of euvolesmic and hypervolemic hyponatremia
- Comparatively response in patients with HF and euvolesma
- Prolonged tolvaptan improves sodium with an acceptable margin of safety

**EVEREST**
- Assessed tolvaptan for worsening heart failure
- No change on long-term mortality or heart failure related morbidity
- Improved patient assessed dyspnea, body weight, and edema
- Similar adverse events

**Conivaptan**
- Three major clinical trials
- Small sample size in all trials (IV and PO)
- IV conivaptan associated with improvement in serum Na⁺ (33% withdrew)
- Increased cardiac adverse events in hypervolemic patients with heart failure

**Potential Safety Issues**
- FDA warning for tolvaptan
  - Serious and potential fatal liver damage
  - Limit use to 30 days
  - Avoid in those with underlying liver disease
  - Discontinue if symptoms of liver injury
  - Liver damage not reported in hyponatremia trials
  - Reported in trial for polycystic kidney disease
  - Reversible upon discontinuation
  - Doses of 120 mg/day
  - Rapid rise in serum sodium
  - Clinical trial data vs real life experience
  - Frequent sodium monitoring, every 4-8 hours during active correction

**Controversies Surrounding Vaptans**
- Transient effect
- Cost
- Hyponatremia costly + increases hospital length of stay
- Vaptans additive cost
- Mortality benefit in heart failure?
- Lack of evidence based clinical trials
- Vaptans vs fluid restriction
- Limited data supporting fluid restriction
- Varying recommendations in guidelines
- Use clinical judgment

**References**
Vaptans in Clinical Practice

- European Guidelines
  - Recommend against vaptans
  - Negative risk benefit ratio
  - No proven benefit aside from increasing Na⁺ concentrations
  - Concern for rapid rise in serum Na⁺
- American Position Statement
  - Prefer traditional treatment with fluid restriction
  - Consider for mild to moderate hyponatremia
  - Must consider cost-benefit ratio
  - Limited duration – limited benefit
  - Should not be used in conjunction with other treatments

Audience Participation #4

- RD is a 70 y/o CF who has been hospitalized for the past three weeks. Initially hospitalized for a hip fracture secondary to a mechanical fall, she has also completed a treatment course for HAP. Acute issues as this time include: hyponatremia secondary to SIADH, delirium, and UTI.
- Na⁺ over the past 5 days: 131 mEq/L, 127 mEq/L, 126 mEq/L, 125 mEq/L, 123 mEq/L (today)
- At which point in treatment of RD’s SIADH would you consider use of tolvaptan?
  - A) First line treatment
  - B) After failed fluid restriction x48 hours
  - C) After failed treatment with hypertonic saline
  - D) After failed treatment with urea

Hyponatremia Treatment in Clinical Practice – Registry Data

- 3087 cases across 225 sites in United States and Europe
  - Hypervolemic (n=1490)
    - HF (n=762)
    - Cirrhosis (n=630)
  - Euvolemic (n=1597)
    - SIADH (n=1524)
    - Other (n=73)
- Initial management
  - Fluid restriction 35%
  - No active therapy 17%
  - 0.9% NaCl 15%
  - Tolvaptan 5%
  - Hypertonic Saline 2%
  - Conivaptan <1%

SIADH Treatment in Clinical Practice – Registry Data

- Initial treatment
  - Fluid restriction 26
  - 0.9% NaCl 23
  - Untreated 11
  - Fluid restriction + 0.9% NaCl 7
  - Tolvaptan 5
  - Salt tabs 4
  - Hypertonic Saline 3
  - 0.9% NaCl + loop diuretic 3
  - Demeclocycline 5
  - Combination of Fluid restriction, hypertonic saline, 0.9% NaCl, loop diuretic, and/or salt tabs 8

Hyponatremia Treatment in Clinical Practice – Registry Data

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>%Patients with Na⁺ &gt; 130 mEq/L at discharge</th>
<th>%Patients with Na⁺ &gt; 135 mEq/L at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>No therapy</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Normal saline</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Hypertonic Saline</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>66</td>
<td>34</td>
</tr>
</tbody>
</table>

Hyponatremia Treatment in Clinical Practice – Registry Data

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>% of patients with overly rapid Na⁺ correction (Δ Na⁺ &gt; 12 mEq/L in any 12 hour period or &gt;18 mEq/L in any 48 hour period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.9%</td>
</tr>
<tr>
<td>No therapy</td>
<td>1.4%</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>1.4%</td>
</tr>
<tr>
<td>Normal saline</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hypertonic Saline</td>
<td>16.0%</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>11.6%</td>
</tr>
</tbody>
</table>
Conclusion

- Sodium and water homeostasis is regulated via osmotic and non-osmotic pathways by aldosterone and vasopressin.
- There are three main types of hypotonic hyponatremia—differentiated by patient’s volume status and clinical presentation.
- The preferred treatment for someone with mild-moderate SIADH is fluid restriction.
- Vaptans may be used for management of euvoletic and hypervolemic hyponatremia in patients failing first line treatment options—cost should be considered.