Clinical Decisions in Hyponatremia

Jonathan M. Pell, M.D.
University of Colorado at Denver Health Sciences Center

Objectives

- Understand the basic physiologic concepts that govern water and sodium balance
- Use concepts to better understand and use urine and plasma electrolyte and osmolarity values
- Review basic approaches to correction of sodium disturbances
- Learn an approach to hyponatremia in the geriatric population
- Learn about new and soon to come treatments for hyponatremia

Why is it important to talk about hyponatremia

- Most common electrolyte derangement
- Portends poor prognosis in CHF and cirrhosis
- Increases mortality (Na <135 vs. 135-144)
  - Increased risk of in hospital mortality (odds ratio 1.47)
  - Increased 1 year mortality (hazard ratio 1.38)
  - Increased 5 year mortality (hazard ratio 1.25)
- Inappropriate treatment can lead to irreversible morbidity

Ref 1, 2, 3, 10
Water problem or sodium problem?

- Majority of Sodium disturbances are due to too much water and rarely due to not enough Sodium
- Most cases of hyponatremia due to sodium loss are due to too much water retention in the setting of sodium loss

Basic Physiology of Sodium Management

- Medullary osmoreceptors stimulate thirst in the setting of increased plasma tonicity
- Osmoreceptors are sensitive to 1-2% changes in plasma osmolality and regulate ADH secretion
- Ventricular and arterial baroreceptors trump osmoreceptors
  - stimulate ADH secretion regardless of plasma tonicity in the setting of arterial underfilling
  - Activate renin-angiotensin-aldosterone system

Framework of Hyponatremic states

Serum Osmolarity
- High (translocational)
  - Hyperglycemia
  - Mannitol
  - Sorbitol/glycine surgical irrigation
- Normal (pseudohyponatremia)
  - Hyperlipidemia
  - Hyperproteinemia
- Low
  - Most common causes

Volume Status
- Hypervolemia (edema states)
  - CHF
  - Cirrhosis
  - Nephrotic syndrome
  - Pregnancy
- Euvolemia
- Hypovolemia

Hypervolemia
- Thyrotoxicosis
- Cortisol osmol osmostat
- SIAD
- Polyuria
- Polydipsia
- Beer potomania

Renal loss
- Diuretics
- Type IV RTA
- Cerebral salt wasting

Urine Na>20
- Diarrhea
- SIAD
- Hemorrhage
- 3rd spacing
- Burns

Algorithms vs. Experts

- 121 subjects with Na <130 and Serum Osms <280
- Three Diagnostic Approaches
  - Algorithm – Junior physician establishes diagnosis using the algorithm in 24 hours
  - Senior Physician - Internal Medicine Generalist or Intensivist without the algorithm established the diagnosis in 24 hours
  - Reference Standard - Endocrinologist with a special interest in hyponatremia had unlimited time and access to patient information to establish the diagnosis


Schrier 2006.
The Winner Is……

- Reference Standard for diagnosis agreed with the Senior Physician 32%
- Reference Standard for diagnosis agreed with the Junior Physician using the algorithm 71%
- Therapeutic consequences were 48% and 86% respectively

Case 1

- 23 yo female with anxiety is found down at home. Family reports that she had recent lethargy and headache, but denies her using illicits. They did state that she has increased her water intake recently to "cleanse her system". Her only medication is imipramine which she has been on for 3 years.

Physical Exam: Wt 60kg Temp 36.8 HR 75 BP 120/70 RR 12
Neuro- Nonfocal but patient is confused and inattentive
Abdomen- Fullness in the suprapubic area

Head CT is neg, Urine tox is pos for THC, and Serum tox screen is neg

Initially obtained Lab values

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<th>Value</th>
<th>Unit</th>
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<tr>
<td>118</td>
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<tr>
<td>85</td>
<td>23</td>
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<tr>
<td>8</td>
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<td>14.7</td>
<td>38.1</td>
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<td>385</td>
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Urine [Na+] - 25 mM/L
Urine osmolality- 130 mOsm/L
Urine [K+] - 5
TSH - 2.5 mIU/L
Diagnosis: Polydipsia

- How much did she have to drink?
  - Normal subjects can excrete 10-15L of free urine/day when maximally diluting their urine to 40-60 Osm/L
  - Unlikely that she drank more than 10-15L/day
  - She is unable to dilute urine below 130mOsm/L
    - only need to drink 5-7L/d which is possible

Treatment for Psychogenic Polydipsia

- Patients will self correct as they have relatively normal ability to excrete a free water load
- Rarely do they have long term neurologic sequelae even when Δ[Na] over 24 hours > 20mM/L
  - Exception is case reports of malnourished alcoholics

Take Home Points

- Don’t be fooled by a high urine osmolarity in polydipsia
- Many antipsychotics and antidepressants
  - Cause syndrome of inappropriate antidiuretic hormone secretion
  - Patients with psychoses seem to have a dissociation between plasma tonicity, thirst and ADH secretion
- Look for exacerbating medications or illicit drugs particularly MDMA in younger patients
Case 2
- 45 yo male with no medical history presents with right sided chest pain and blood streaked sputum. He reports a month of night sweats and 10lb wt loss. He denies excessive thirst or water intake, and he denies neurological deficits.
- Wt 70kg Temp 37.6 HR 68 BP 125/75 RR 12
- Orthostatics unremarkable but exam reveals supraclavicular and axillary lymphadenopathy
- CXR reveals right hilar mass which is confirmed by CT scan

Initially obtained Lab values
- 122
- 95
- 7
- 77
- 14.7
- 385
- 4.5
- 22
- 0.6
- 10.9
- 43.1
- LDH – 224 U/L
- Uric Acid – 2.6 mg/dL
- LFT’s- WNL
- TSH – 1.87 mIU/L

Initial treatment Plan
- Surgical consultation for supraclavicular lymph node resection for malignancy evaluation
- NPO overnight for surgical procedure in the morning and monitor I/O’s
- IVF fluids-D5Normal saline 0.9% at 125cc/hr for a total of 1 liter while pt is NPO for the procedure and drank 1 liter of fluid orally prior to midnight as he knew he was not going to be able to drink the next morning
Labs the next morning

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<td>4.2</td>
<td>22</td>
<td>0.7</td>
<td>10.8</td>
<td>42.2</td>
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Urine Osm - 864
Serum Osm - 244
Urine [Na] – 100mM/L
Urine [K] – 50mM/L
Urine output 1000cc

Diagnosis → Syndrome of Inappropriate anti-diuresis (SIAD)

- Diagnostic Criteria
  - Clinical euvolemia or hypervolemia
  - Serum Osm < 275mOsm/L
  - Urine Osm > 200mOsm/L
  - Urine Na > 30-40 (depending on Na intake)
  - Normal thyroid/adrenal function, no diuretics
    (supporting evidence is also low uric acid <4mg/dL and low BUN <5)
- Problem- Negative Solute balance
  - Serum Na will continue to fall with the administration of oral or IV fluids with lower osmolarity than the urine

Causes of SIADH

- Cancer - pulmonary, mediastinal, GI, lymphomas, sarcomas
- CNS Disorders - psychosis, mass lesions, inflammatory and demyelinating diseases, trauma, hemorrhage, stroke, infection
- Drugs - desmopressin, oxytocin, nicotine, phenothiazines, SSRIs, opiates, tricyclics, clofibrate, carbamazepine, chlorpropamide, cyclophosphamide, vincristine, MDMA, prostaglandin synthesis inhibitors
- Pulmonary disorders - infection, acute respiratory failure, positive pressure ventilation, asthma, cystic fibrosis
- Miscellaneous - pain, nausea, post-operative state, HIV, endurance exercises, general anesthesia

Understanding the Physiology

- **Problem**
  - There are lots of exceptions to the rules
  - Some variables can't be calculated (e.g., insensible fluid loss)
  - Urine and serum electrolytes not in steady state

- **Solution**
  - Understand concepts and make educated guesses

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How much water retention?

0.60 (TB water %) x 70 (pt wt kg) = 42.00 L

42L x 122 mEq/L (plasma [Na+]) = 5124 mEq of TB solute

If the drop in sodium is due to solute-free water retention

\[
\frac{5124 \text{ mEq TB solute}}{115 \text{ mEq/L (plasma [Na+]})} = 44.55 \text{ L (TB water)}
\]

If the patient was only given 1L IV NS (154mEq/L) and took in 1 liter of free water orally and put out 1L of Urine, why does his new serum sodium suggest that he was given 2.55L of free water?

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\[
100 \text{ mEq/L} + 50 \text{ mEq/L} < 150 \text{ mEq/L} > \text{plasma [Na+]}
\]

Urine Osm- 864
Serum Osm- 244
Urine [Na] – 100mM/L
Urine [K] – 50mM/L

Urine output 1000cc
How much free water is he retaining?

Clearance of free water equation

\[ CH20 = V \times (1 - \frac{UNa+UK}{PNa}) \]

\[ CH20 = 1L \times 1 - \frac{(100+50)}{115} \]

\[ CH20 = -304ml \]

Bottom line

- Every 1L Urine made → 304ml of free water will be retained
- 100% of water given with osmolarity lower than urine will be retained

Treatment Decisions for SIAD

- Degree of Hyponatremia
  - [Na] = 110-115, ?125
- Acute or Chronic
- Symptomatic vs. Asymptomatic
  - Mild symptoms (lethargy, headache, malaise)
  - Severe symptoms (delirium, seizure, coma)

Chronic vs. Acute

- Chronic defined as >48 hours
- Chronic is high risk for central pontine and extrapontine myelinolysis
  - Myelinolysis is characterized by period of improvement with improved serum sodium then mutism, dysarthria, and quadraparesis
  - Balance with risks of hyponatremic encephalopathy

Algorithm for the Treatment of Hyponatremia Associated with SIAD

Rate of correction of Serum [Na+]

- Raise the [Na+] by 1-2 mEq/h but do not exceed 8-12mEq change in a 24h period and no more than 18mEq in 48h
  - Except in malnourished alcoholics and the elderly use 6 - 8mMol/L in a 24h period
- Once serum [Na+] >120, no reason to continue 3% saline unless the patient remains symptomatic
- Proposed formula for correction by Androge et al.
  \[
  \Delta [\text{Na}] / \text{Infusate} = \text{Infusate} [\text{Na}+K] - \text{Serum} [\text{Na}]
  \]
  \[
  \text{Total body water + 1}
  \]

Fear of Math Approach

- IF hyper or euvolemic hyponatremia and Uosm>200
  - w/ severe symptoms (delirium, seizure or coma)
  - or
  - w/ plasma [Na] <110
- THEN Infuse 3% saline at 1-2ml/kg/h
  - May give furosemide 20mg IV to promote free water excretion and limit extracellular volume expansion (Lasix makes the urine ½ NS)


Back to our patient

- [Na] was 115 but he was asymptomatic
- Pt was fluid restricted and given lasix
- He put out 1L urine with repeat electrolyte panel:
  - (Urine was about 1/2 NS)
  - U[Na] + U[K] = 70 < P[Na]
  - Now we could give 0.9%NS and Lasix
  - Plasma [Na] increased 5-7mM/L/d

Take Home Points

- If concern for SIADH, no NS trial unless UOsm <500mOsm/L
- If U[Na] + U[K] >> P[Na] then fluid restriction alone will not raise P[Na]
- When to use 3% saline
  - P[Na]< 115 and mod sx (especially if acute Δ)
  - P[Na]< 125 and severe sx
Case 3

- 75 yo male is brought to the ED for increasing confusion and lethargy. The patient reported diarrhea for the past 4 days without N/V and has been drinking plenty of fluids but not eating well. He has been losing weight slowly since his wife died 3 months ago. His only medical history is some mild HTN for which he takes HCTZ.

Wt 50kg Temp 37.5 HR 88 BP 110/60 RR 12 No orthostasis PE reveals temporal wasting, dry mucous membranes, and no axillary sweat. No lower extremity edema or elevated jugular venous pulsations.

CT scan of the head shows only mild prominence of gyri and sulci consistent with mild atrophy.

Initially obtained Lab values

- Urine [Na+] - 30 mM/L
- Urine osmolarity - 280 mOsm/L
- Serum osmolarity - 250 mOsm/L
- Urine [K+] - 40
- TSH – 1.9 mIU/L
- Albumin- 3.9

Hyponatremia in Geriatrics

Often multifactorial and a process of elimination
Back to our Framework

Serum Osmolarity

High (translocational)
- Hyperglycemia
- Mannitol

Normal
- Hypoproteinemia

Low
- Most common causes

Volume Status

Hypervolemia (edema states)
- CHF
- Cirrhosis
- Nephrotic syndrome
- Pregnancy

Euvolemia
- Hypothyroidism
- Cortisol reset osmostat
- SIAD
- Polydipsia
- Beer potomania

Hypovolemia

Renal loss (urine Na>20)
- Diuretics
- ACE I, ARB
- Type IV RTA
- Central salt wasting

Extrarenal loss
- Diarrhea
- Vomiting
- Hemorrhage
- 3rd spacing
- Burns

Unlikely causes

- Pt is hypotonic since serum Osm = 250
- Albumin is normal with no signs of edema or intravascular volume overload so volume status is not high
- TSH is normal and potassium not high so unlikely thyroid disease, type IV RTA or AI
- Head CT is negative so unlikely cerebral salt wasting due to subarachnoid hemorrhage
- UOsm >100 suggest no psychogenic polydipsia
- No burns, bleeding, or third spacing

Geriatric hyponatremia

- What we know about likely contributors
  - He is on a thiazide diuretic
  - He does have diarrhea and may be hypovolemic w/o being orthostatic
  - Despite a low plasma sodium, ADH is on since Uosm are 280mOsm/L
    - Could be arteriolar filling trumping plasma tonicity
  - Weight loss and mostly liquid diet concerning for poor solute intake
Framework of Hyponatremic states

Serum Osmolarity

- High
  - Hyperglycemia
  - Mannitol
- Normal (pseudohyponatremia)
- Low
  - Most common causes

Volume Status

- Hypervolemia (edema states)
  - CHF
  - Cirrhosis
  - Neprhotic syndrome
  - Pregnancy
- Hypovolemia
- Euvolemia
  - ↓ thyroid
  - ↓ cortisol
  - Reset osmostat
  - SIAD
  - Polydipsia
  - Beer potomania
  - Tea and toast
- Renal loss
  - Urine Na>20
  - Diuretics
  - ACE-I, ARB
  - Type IV RTA
  - Cerebral salt wasting
- Extrarenal loss
  - Urine Na<10
  - Diarrhea
  - Vomiting
  - Hemorrhage
  - Third spacing

How to figure out which is the cause

- Treat them all
- Remember top three rules of geriatrics
  1. First do not harm
  2. Take a really good social history
  3. Top three of your differential diagnoses are medications, medications, and multifactorial

How do we do that?

- SIAD - Give trial of 1 liter of 0.9%NS over the next 24 hours and check Na every 6h since UOsms < 500mOsm/L
- Tea and toast - give oral electrolyte containing fluids
- Diarrhea - Hyponatremia should resolve with Na and volume repletion and get serum uric acid to differentiate b/w SIADH and volume depletion
- Diuretic use – hold the HCTZ
- Beer potomania – take a history but Rx same as tea and toast
- Reset osmostat – No therapy necessary
"Beer potomania" and 
"tea and toast diet"
- Normal subjects excrete ~ 750 mOsm solute/day
  - Can dilute urine to 60 mOsm/L so even if 
    taking in 12.5L of free water/day all can be 
    excreted
  - If daily solute intake and excretion drops 
    below 240 mOsm
  - At max dilution capacity of 60 mOsm/L can 
    only drink 4 L free water before kidney is 
    overwhelmed
  - Easily corrected with improve solute intake

Thaler SM; Teitelbaum I; Berl T. "Beer potomania" in non-beer drinkers: effect of low dietary solute 

Take home points
- Thiazide diuretics make U[Na] measurement useless
- Hyponatremia is often multifactorial in 
  the geriatric population and these 
  patients are at the highest risk for harm
- Use serum uric acid to help differentiate 
  SIADH from appropriate ADH secretion 
  in volume depletion

The Old and New of ADH antagonists

The Future of Hyponatremia Treatment
### The Old

<table>
<thead>
<tr>
<th>Drug (route of admin)</th>
<th>Class/Use</th>
<th>ADH affect</th>
<th>Hyponatremia setting studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium Carbonate (PO)</td>
<td>Heavy Metal Bipolar Disorder</td>
<td>Interferes with ADH stimulated cAMP production in collecting tubule cells</td>
<td>No longer in use for hyponatremia but rarely used in CHF</td>
</tr>
<tr>
<td>Demeclocycline (PO)</td>
<td>Tetracycline antibiotic/Infection and SIADH</td>
<td>Inhibits ADH effect on renal tubules</td>
<td>Unlabeled use for chronic SIADH at high doses</td>
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</table>


### The New

<table>
<thead>
<tr>
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<th>Class/Use</th>
<th>ADH affect</th>
<th>Hyponatremia setting studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan (IV and PO)</td>
<td>Vaptan/hyponatremia</td>
<td>V1a and V2 receptor antagonist</td>
<td>IV formulation is FDA approved for moderately symptomatic hyponatremia, being studied in CHF</td>
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<tr>
<td>Tolvaptan (PO)</td>
<td>Vaptan/hyponatremia</td>
<td>V2 receptor antagonist</td>
<td>FDA approved for hypervolemic and euvolemic hypernatremia in CHF, cirrhosis and SIADH</td>
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<td>Satavaptan (PO)</td>
<td>Vaptan/hyponatremia</td>
<td>V2 receptor antagonist</td>
<td>Not clinically available, studied in SIADH, CHF, and now prevention of ascites in cirrhosis</td>
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<tr>
<td>Lixivaptan (PO)</td>
<td>Vaptan/hyponatremia</td>
<td>V2 receptor antagonist</td>
<td>Not clinically available, studied in SIADH, cirrhosis, and CHF</td>
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### References