Disorders of Plasma Sodium Concentration

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Salt and Water

- Approx 60% of body weight is salt water
- Blood sodium concentration ([Na⁺]) is approximated by the ratio of total body sodium to total body water, i.e.
  \[ \text{Blood (plasma or serum)} \ [\text{Na}+] = \frac{\text{Total body sodium}}{\text{Total body water}} \]
- Most disorders of sodium concentration are primarily due to alterations in water balance.

Water Balance

- Hyponatremia is defined as a plasma (or serum) sodium concentration ([Na⁺]) of < 135 mEq/L. Hypernatremia is defined as a plasma sodium concentration ([Na⁺]) of > 145 mEq/L.
  - In steady state, water intake = water output
  - Water excess without a change in total body sodium content leads to a decrease in blood sodium concentration (hyponatremia)
  - Water deficit without a change in total body sodium content leads to an increase in blood sodium concentration (hypernatremia)
Physiologic Regulation of Serum Sodium Concentration [Na+] 

- ↑ water intake → ↓ [Na+] → ↓ antidiuretic hormone (ADH) release and thirst → ↑ renal water excretion and ↓ water intake → normalization of [Na+]

- ↓ water intake → ↑ [Na+] → ↑ ADH and thirst → ↓ renal water excretion and ↑ water intake → normalization of [Na+]

Regulation of ADH (1)

- ADH, also called arginine vasopressin (AVP), an octapeptide synthesized by the hypothalamus and stored and secreted by the posterior pituitary.
- ADH acts on the distal tubule collecting duct to increase water reabsorption and thus decrease renal water excretion. In the presence of substantial amounts of ADH the urine will be concentrated (urine osmolality > plasma osmolality).

Regulation of ADH (2)

- Physiologically regulated by osmotic and non-osmotic factors.
- A small (1-2%) increase in effective osmolality ([Na+] + [glucose]) will lead to thirst and increase ADH release. Both thirst and ADH are triggered at a plasma osmolality of about 280 mmol/kg and shut off at lower plasma osmolality.
- A large (approx 10%) decrease in blood volume or blood pressure will also increase ADH release and can override the effect of osmolality. This is called non-osmotic stimulation of ADH release.
- ADH release can also be affected by other non-osmotic stimuli (e.g., drugs, pain, stress).
Osmotic vs. non-osmotic regulation of ADH

Effect of ADH on urine osmolality and volume

<table>
<thead>
<tr>
<th>ADH</th>
<th>Urine osmolality (mmol/Kg)</th>
<th>Urine volume (L/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>++</td>
<td>400</td>
<td>1.5</td>
</tr>
<tr>
<td>++++</td>
<td>1200</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Note: Calculations assume that there is excretion of 800 mmol of solute per day.
Plasma sodium concentration

- Plasma sodium concentration is approximated by the ratio of total body sodium to total body water, i.e.
  \[
  \text{Plasma or serum } [\text{Na}^+] = \frac{\text{Total body sodium}}{\text{Total body water}}
  \]
- Since sodium is a univalent ion, plasma \([\text{Na}^+]\) can be expressed as mmol/L or mEq/L

How are total body sodium and water determined?

- We do not measure total body sodium or total body water in clinical practice.
- Therefore, when evaluating disorders of sodium concentration, the clinician must decide if total body sodium and/or water are high, normal, or low! This is assessed by history, physical examination, and laboratory values.

Hyponatremia

Hyponatremia = decreased plasma sodium concentration ([Na+] = excess of total body water (TBW) relative to total body sodium (TBNa+). Some examples:
1. ↑ TBW with normal TBNa+ . Example: SIADH
2. ↓ TBW with ↓ TBNa+ . Example: Diuretic ingestion coupled with water intake.
3. ↑↑ TBW with ↑ TBNa+. Example: edematous disorders, i.e. congestive heart failure (CHF), liver cirrhosis, renal failure, coupled with water intake.
Pathophysiology of Hyponatremia (1)

- Physiology
  - Normal kidneys can excrete a large amount of dilute urine.
  - In the absence of ADH, urine osmolality can be as low as 50 mmol/L.
  - The daily solute load is generally 600-1200 mmol/day.
  - Even if urine osmolality excretion is relatively low (600 mmol/day), then 12 L/day of maximally dilute urine can be excreted.
  - Thus sustained hyponatremia due to fluid ingestion alone is very rare, providing solute intake is maintained.

Effect of ADH on urine osmolality and volume

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Note: Calculations assume that there is excretion of 600 mmol of solute per day.

Pathophysiology of Hyponatremia (2)

- Pathophysiology
  - Hyponatremia therefore almost always indicates impaired renal water excretion. This may be due to:
    - Decreased solute excretion. Example: beer drinkers, who ingest much fluid but very little (i.e. 100-200 mmol/day) solute ("beer drinker’s potomania"). A similar syndrome occurs in any patient with poor solute but adequate fluid intake ("tea and toast diet")
    - Impaired urinary dilution, due to:
      - Excess ADH production
      - Intrarenal factors (independent of ADH).
Beer drinker’s syndrome

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<th>Urine volume (L/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Calculation assumes that there is excretion of 200 mmol of solute per day.

Intrarenal Factors Affecting Water Excretion

- Normal ability to excrete water depends on 3 factors:
  1. Filtration of solute by the glomeruli
  2. Delivery of solute to distal (diluting) nephron sites
  3. Reabsorption of solute but not water in the distal nephron (when ADH is suppressed)
Pathophysiology of Hyponatremia (3)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Decreased filtration of solute</th>
<th>Increased solute reabsorption in proximal nephron</th>
<th>Decreased solute reabsorption in distal nephron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Decreased GFR</td>
<td>Reduced renal blood flow resulting in stimulation of proximal solute reabsorption</td>
<td>Inhibitors of solute reabsorption in distal nephron</td>
</tr>
<tr>
<td>Example</td>
<td>Renal failure</td>
<td>Congestive heart failure</td>
<td>Thiazide diuretics</td>
</tr>
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</table>

Volume status (1)

- Total body water is divided into intracellular fluid (ICF) and extracellular fluid (ECF).
- Sodium is present in high concentrations in the ECF but only in low concentrations in the ICF.
- Clinically, it is usually ECF volume that is detected, and thus when we say “volume”, we generally mean ECF volume, which is dependent on total body sodium content.

Volume status (2)

- Hypovolemia: low total body sodium (ECF volume)
  - Flat neck veins
  - Decreased skin turgor
  - Orthostatic changes in heart rate and blood pressure (increase in heart rate and decrease in blood pressure with standing)
- Hypervolemia: high total body sodium (ECF volume)
  - Edema
- Euvolemia: no findings of either hypovolemia or hypervolemia
**Volume depletion vs. dehydration**

A 70-kg man has a TBW of 0.6 x 70 kg = 42L, of which about 2/3 is in the ICF and 1/3 in the ECF (the ECF is about 1/5 plasma and 4/5 interstitial fluid).

<table>
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<tr>
<th>ICF</th>
<th>ECF</th>
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<tr>
<td>28L</td>
<td>14L</td>
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Loss of 3L of ECF results in a 21% decrease in ECF volume, resulting in symptoms and signs of hypovolemia. However loss of 3L of TBW results in a 2L decrease in ICF and only a 1L (7%) decrease in ECF, and there are no symptoms or signs of hypovolemia.

**Volume status (3)**

- Water depletion alone will only lead to clinically-evident hypovolemia if it is very severe. This is not common.

**Etiology of Hyponatremia (1)**

- Hypovolemic hyponatremia = decrease in TBNa+ (ECF volume)
  - Flat neck veins, decreased skin turgor, orthostatic hypotension
  - Renal Na+ losses – diuretics, primary adrenal insufficiency (Addison’s disease), salt-wasting nephropathies
  - Extrarenal Na+ losses – diarrhea, vomiting, excessive sweating
- Euvolemic hyponatremia = normal TBNa+ (ECF volume)
  - SIADH = most commonly due to (1) tumor (2) pulmonary disease (3) central nervous system disease
  - Hypothyroidism
  - Psychogenic polydipsia
  - “Beer drinker’s potomania”
- Hypervolemic hyponatremia = increased TBNa+ (ECF volume)
  - CHF
  - Liver cirrhosis
  - Renal failure
Etiology of Hyponatremia (2)

- Clinical evaluation involves history and physical examination as well as urine chemistries
  - Low UNa+ (< 10 mmol/L) suggests extrarenal loss of Na+ or edematous disorder (in which kidneys are avidly reabsorbing sodium, and thus causing edema, usually due to a decrease in effective circulatory volume);
  - "Normal" UNa+ (>20 mmol/L) suggests renal loss of Na+ or excess ADH in the absence of renal sodium avidity, as in SIADH.

Treatment of Hyponatremia

- Hypovolemic hyponatremia – physiologic saline
- Hypervolemic hyponatremia – fluid restriction and diuretics.
- Euvolemic hyponatremia (e.g., SIADH):
  - Mild asymptomatic hyponatremia should be considered a diagnostic clue but does not mandate treatment.
  - More severe asymptomatic hyponatremia (i.e., serum sodium < 125 mmol/L) should be treated with water restriction.
  - Symptomatic hyponatremia (confusion, seizures, coma due to hyponatremia) is considered a medical emergency and generally requires hypertonic saline with or without diuretics. Avoid rapid or overcorrection!
Hypernatremia

Hypernatremia = increased [Na+] = decrease in total body water (TBW) relative to total body sodium (TBNa+).

1. ↓ TBW with normal TBNa+. Examples: (1) patients with decreased thirst or inability to drink water; (2) diabetes insipidus (DI), in which ADH release is impaired or absent (central DI) or the kidney does not respond to ADH (nephrogenic DI).

2. ↓↓ TBW with ↓ TBNa+. Example: diuretics without concomitant water ingestion.


Pathogenesis of Hypernatremia

- In the presence of ADH, normal kidneys can concentrate urine to a urine osmolality of 1200 mmol/L.
- Thus, if the daily solute load is 600 mmol/day, urine output can be as low as 500 mL/day.
- These low urinary volumes will minimize renal water loss if water intake is impaired.
- However, remember that insensible water loss (primarily via respiration) is about 500–700 mL/day. Therefore, even when there is maximum antidiuresis, total cessation of water intake will lead to hypernatremia.

Etiology of Hypernatremia

- Hypovolemic hypernatremia = decrease in TBNa+
  - Renal Na+ losses = diuretics (with inadequate water intake), osmotic or post-obstructive diuresis, tubular injury
  - Extrarenal Na+ losses = sweating, diarrhea, vomiting (with inadequate water intake).
- Euvolemic hypernatremia = decrease in TBH2O
  - Central diabetes insipidus (trauma, idiopathic, tumor)
  - Nephrogenic diabetes insipidus (congenital, drugs, hypercalcemia, tubular disease)
  - Decreased thirst, water intake (“nursing home syndrome”)
- Hypervolemic hypernatremia = increase in TBNa+
  - Hypertonic fluid administration
  - Mineralocorticoid excess states
  - Salt poisoning (and seawater ingestion)
Treatment of Hypernatremia

• **Hypovolemic hypernatremia** – hypotonic fluids.
• **Euvolemic hypernatremia** -- water administration (+ ADH in central DI)
• **Hypervolemic hypernatremia** can be problematic. If severe, it may require both water administration plus either diuretics or dialysis to remove the excess sodium.
• Rate of correction should not exceed 0.5 mEq/L/hr, as too rapid a reduction in serum sodium and osmolality may result in shift of water into the brain and brain edema.

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Patient 1

• A 60 year old man with known lung cancer presents with fatigue and cough. On exam his vital signs are normal. He is not orthostatic. His jugular veins are visible but not distended, skin turgor is normal, and he has no edema. He is alert and oriented and answers questions appropriately. Chest X-ray shows a R lower lobe infiltrate. Plasma electrolytes (in mmol/L) are: Na 114, K 4, Cl 80, CO2 24. The plasma urea nitrogen and creatinine are 6 and 0.6 mg/dL, respectively. The urine osmolality is 500 mmol/L.
What is the most likely diagnosis?
A. Beer drinker’s syndrome
B. Psychogenic polydipsia
C. Addison’s disease
D. SIADH

How do you treat the hyponatremia?
A. Isotonic saline
B. Hypertonic saline
C. Tolvaptan
D. Fluid restriction

Patient 2
- An 85-year-old woman with Alzheimer’s dementia is admitted from a nursing home for obtundation. On examination she has hypotension (BP 80/50 mmHg), flat neck veins, clear chest, and no edema. Chest X-ray is clear. Plasma electrolytes (in mmol/L) are: Na 164, K 4, Cl 130, CO2 24. The plasma urea nitrogen and creatinine are 16 and 1.2 mg/dL, respectively. The urine osmolality is 500 mmol/L.
What is your diagnosis?

A. Dehydration
B. Volume depletion

How do you initially treat this patient?

A. Isotonic saline
B. Hypotonic saline
C. Dextrose in water
D. Oral water replacement