Effective Treatment of Hyponatremia: Managing Acute and Chronic States While Avoiding Harm

Hyponatremia (defined as serum sodium less than 135 mmol/L) is a commonly encountered disorder that if left untreated, may result in severe consequences. There are multiple causes of hyponatremia, some of which include excessive water intake, inability of the kidney to excrete water, and overuse of thiazide diuretics. Certain populations are at an increased risk of developing hyponatremia, including those with cardiac, hepatic, or renal dysfunction leading to excessive ADH release. This issue of CLIPS briefly summarizes an article that reviews the treatment of both acute and chronic hyponatremia, emphasizing against raising serum sodium concentrations too rapidly. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Hyponatremia: Definitions
- Symptomatic hyponatremia – severe signs or symptoms of cerebral edema (i.e., a medical emergency).
- Asymptomatic hyponatremia – lacking serious signs or symptoms of cerebral edema.

Key Diagnostic Steps When Deciding to Treat
The following is the clinical approach that should be taken when managing patients with hyponatremia:
1. Measure serum osmolality to confirm a true hypo-osmolar state (ie, < 275 mOsm/kg).
2. Assess patient for symptoms such as visual changes or encephalopathy which suggest cerebral edema.
3. Determine the duration of hyponatremia (shorter or longer than 48 hrs). This determines the rate of correction.
4. Assess for proper urinary dilution by checking urine osmolality. (appropriate urine dilution < 100 mOsm/kg)
5. Determine if hyponatremia resulted from underlying causes (i.e., glucocorticoid deficiency).
6. Assess patient’s medications and nutritional intake for excess water consumption.
7. Assess patient's medications for drug that may potentiate ADH effects (i.e., SSRIs).

Treatment of Hyponatremia with Serious Signs or Symptoms (Symptomatic)
- In symptomatic hyponatremia, patients’ require rapid correction as this is a medical emergency.
- The goal of initial therapy is to correct cerebral edema.
- Initial treatment should consist of 3% saline at a rate of 1 ml/kg/hr which should raise serum sodium concentrations by approximately 1 mmol/L/hr. The infusion should be discontinued when symptoms resolve.
- Those patients with hypervolemic hyponatremia should also receive a loop diuretic in addition to 3% saline to prevent volume overload.
- After symptoms resolve, the appropriate rate of correction should be determined, as too rapid correction can result in osmotic demyelination syndrome.
- Serum sodium concentrations should not be raised by more than 10 – 12 mmol/L in the first 24 hours and no more than 18 mmol/L in the first 48 hours. Do not try to correct sodium to normal values.
- Patients with acute hyponatremia may tolerate complete correction; however, evidence suggests that this is not advantageous.
- Patients with chronic hyponatremia should have their sodium corrected at a slower rate than those with acute hyponatremia. Some sources recommend correction rates of less than 10 mmol/L.
- If serum sodium concentrations have been overcorrected, desmopression is effective in lowering serum sodium. Water, with or without desmopression, can also be administered to lower sodium concentrations.

CONTINUED NEXT PAGE
Various formulas exist to calculate the change in serum sodium concentrations (e.g., Androgué-Madias formula and Barsoum-Levine equation) while correcting hyponatremia; however, they should only be used as guides and should never replace strict electrolyte monitoring.

**Treatment of Hyponatremia without Serious Signs or Symptoms (Asymptomatic)**
- Asymptomatic hyponatremia does not require rapid correction of serum sodium concentrations.
- Initial management should include evaluating for reversible causes of water excess. These causes may include administration of hypotonic fluids or medications such as NSAIDs that block water excretion.
- The patient must also be evaluated for underlying disease states such as CHF, hypothyroidism, or adrenal insufficiency which may cause excess water retention.
- If hyponatremia cannot be corrected by stopping reversible causes or by treating underlying disease states, treatment can be started based on the patient’s extracellular fluid volume status:

<table>
<thead>
<tr>
<th>Extracellular Fluid Volume Status</th>
<th>Initial Treatment of Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Fluid and sodium restriction, loop diuretic</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>I.V. 0.9% saline, discontinue diuretics</td>
</tr>
<tr>
<td>Euvolemic</td>
<td>Fluid restriction, loop diuretics ± salt tablets, dietary sodium augmentation, demeclocycline, vasopressin antagonists</td>
</tr>
</tbody>
</table>

**Pharmacological Inhibition of Vasopressin**
- Patient compliance often becomes an issue with fluid restriction. Sometimes fluid and sodium restrictions alone are not effective in managing hyponatremia. In these two instances, drugs that inhibit vasopressin can be added to the regimen to aid in correcting sodium concentrations.
- Demeclocycline and lithium inhibit the effects of ADH in the kidney. Demeclocycline is preferred over lithium because of the nephrotoxicity associated with lithium. Demeclocycline in doses of 300 to 600 mg twice daily begin to enhance free water excretion in one to two weeks. Importantly, demeclocycline is contraindicated in children and pregnant females.
- Drugs that block the vasopressin subtype 2 (V2) receptor (known as “vaptans”) increase free water excretion in the kidney which makes them useful for treating certain types of hyponatremia.
- Tolvaptan (Samsca®) is an oral V2 antagonist approved for the treatment of euvolemic and hypervolemic hyponatremia. In studies, tolvaptan has not been shown to reduce rates of rehospitalization or death in patients with congestive heart failure, but it has been shown to improve sodium concentrations, overall fluid balance, and symptoms of congestion. Daily doses range from 15 to 60 mg once daily.
- Conivaptan (Vaprisol®) is an intravenous V1a and V2 antagonist approved for the treatment of euvolemic and hypervolemic hyponatremia. Its use has been limited to 4 days because of its ability to inhibit CYP 3A4 leading to many drug interactions. The recommended dose is a 20 mg bolus infused over 30 minutes followed by continuous infusions of 20 to 40 mg daily.
- Other V2 antagonists include lixivaptan (VPA-985) and satavaptan (Aquilda®).
- Most studies suggest that V2 antagonists provide slow, reliable increases in serum sodium. However, definitive recommendations for therapy are still needed. Cost is also an issue with V2 antagonists. Tolvaptan costs approximately $250 per tablet.

**Therapy in Specific Disease States**
- Patients with hyponatremia and cirrhosis should be treated with water and salt restriction along with loop diuretics and aldosterone antagonists. Tolvaptan has also been efficacious in correcting serum sodium concentrations in patients with cirrhosis.
- Patients with hyponatremia and SIADH should be treated with water restriction and adequate nutritional intake. Demeclocycline, tolvaptan, or loop diuretics with salt tablets may also be useful in this population.
- Patients with mild exercise-associated hyponatremia should be treated with fluid restriction and clinical observation, while avoiding saline infusions. If severe (< 120 mmol/L), hypertonic saline is preferred.