Hyponatraemia: Is it clinically relevant?

Miriam Giordano Imbroll  MD, MRCP (UK), Cert. RCP (Endocrinology and Diabetes) (UK)

Department of Medicine, Faculty of Medicine and Surgery, University of Malta, Msida, Malta; Department of Medicine, Mater Dei Hospital, Msida, Malta.
Email: giordanomiriam@yahoo.com

Educational aims
• To highlight the importance of treating hyponatraemia, even if chronic and not associated with obvious clinical features
• To increase familiarity with the common causes and diagnosis of hyponatraemia
• To update the knowledge on management of hyponatraemia including the use of novel drug therapy

Key words
Hyponatraemia, hypotonic hyponatraemia, Syndrome of inappropriate antidiuresis, demeclocycline, vaptans.

Abstract
Hyponatraemia, defined as a sodium concentration <135mmol/l, is the most common electrolyte imbalance encountered in clinical practice. Symptoms can range from seemingly asymptomatic to severe and even life-threatening. Hyponatraemia is usually managed by clinicians from various fields, leading to a wide variety of approaches to its diagnosis and treatment.

Introduction
Hyponatraemia is the commonest electrolyte imbalance in clinical practice. It is defined as a sodium concentration of less than 135mmol/l. In 2014, Clinical Practice Guidelines on the diagnostic approach and treatment of hyponatraemia were published as a joint venture of 3 major European societies representing specialists with a natural interest in hyponatraemia. The American recommendations on diagnosing, evaluating and treating hyponatraemia, published in 2013, are similar in many aspects, but they do differ in others, especially in management. This article reviews the diagnosis and management of hyponatraemia according to the European Clinical practice guidelines, highlighting any discrepancies between the European and American views.

Pathophysiology
Hyponatraemia is primarily a disorder of water balance, with a relative excess of body water compared to total body sodium and potassium content. The major mechanisms responsible for regulating water metabolism are thirst and the pituitary secretion and renal effects of arginine vasopressin (AVP; antidiuretic hormone, ADH). When serum osmolality starts to rise, osmoreceptive neurons located in the anterior hypothalamus detect a decrease in cell stretch which in turn leads to increased thirst and increased release of AVP from the posterior pituitary gland. In the left atrium, carotid sinus and aortic arch, there are stretch-sensitive receptors (baroreceptors) that sense circulating volume. When the volume decreases, afferent neural impulses decrease and AVP secretion increases. AVP, then, regardless of the stimulus, binds to the AVP V2 receptor subtype in the collecting duct of the kidney and activates the signal transduction cascade resulting in antidiuresis, with urine being more concentrated.

Classification of hyponatraemia
There are three classifications of hyponatraemia based on:
1. Severity;
2. Symptoms;
3. Rate of development.

The first classification is based on the level of serum sodium, with cut-offs below 125mmol/l regarded as profound, levels...
between 125 and 129 mmol/l moderate and levels above 130 mmol/l being mild.

Symptoms can range from seemingly asymptomatic, with subtle clinical findings such as a gait disturbances, falls, mild cognitive deficits5 and osteoporosis to more severe. In one study, the prevalence of hyponatraemia in a group of patients with a verified bone fracture was significantly higher than a control group who had no history of bone fracture6. In another study it was found that the occurrence of all forms of hyponatraemia on admission were associated with increased in-hospital mortality and added pressure on the hospital’s limited resources. Moderately severe symptoms include confusion, nausea or headache whereas severe symptoms may include vomiting, seizures or coma. Symptoms are very non-specific, so a diagnosis of hyponatraemia should not rely on symptoms alone.

The third classification is based on the time of development, with 48 hours being the cut-off for differentiating acute from chronic. This classification is based on the fact that in the presence of hypotonic hyponatraemia, water shifts from the hypotonic extracellular to the intracellular compartment across an osmotic gradient, causing brain oedema. This is associated with the severe symptoms of hyponatraemia. This seems to occur more frequently when hyponatraemia develops in less than 48 hours because the brain has had too little time to adapt to its hypotonic environment. After 24 to 48 hours, the brain reduces the number of osmotically active particles within its cells, mainly potassium and organic solutes in an attempt to restore brain volume.8

**Pitfalls in diagnosis**

Once biochemical hyponatraemia is confirmed, non-hypotonic hyponatraemia should be excluded. One of the commonest causes is hyperglycaemia. When solutes which are impermeable to the cell membrane are present in excess in the extracellular compartment, an osmotic pressure gradient is created across the cell membranes, leading to osmotic movement of water from the intracellular to the extracellular compartment. This causes dilutional hyponatraemia with a water shift from the intra to the extracellular compartment, so posing no risk of brain oedema. Pseudohyponatraemia is a laboratory artefact that occurs when an abnormally high concentration of serum lipids or proteins interfere with the accurate measurement of sodium9.

**Differentiating causes of hypotonic hyponatraemia**

Once hypotonic hyponatraemia is confirmed, measurement of a spot urine osmolality and sodium will help diagnose the cause of hyponatraemia (Figure 1).

**Treatment of hypotonic hyponatraemia**

**Acute and/or symptomatic hyponatraemia**

If hyponatraemia is associated with symptoms, treatment should be initiated immediately and this involves the infusion of 3% hypertonic saline. Hypertonic saline is listed as a high alert medication by the institute for safe medication practice (ISMP)10. Such drugs bear a heightened risk of causing significant patient harm when used in error. Preparing this infusion takes time and meticulous

**Figure 1: Clinical practice guideline on diagnosis and treatment of hyponatraemia**

- **Hyponatraemia**
  - Exclude hyperglycaemia and other causes of non-hypotonic hyponatraemia
  - Hypotonic hyponatraemia
    - Acute or severe symptoms?
      - Yes
        - Consider immediate treatment with hypertonic saline (Section 7)
      - No
        - Urine osmolality
          - ≤ 100 mOsm/kg
            - Consider
              - Primary polydipsia
              - Low solute intake
              - Beer potomania
          - > 100 mOsm/kg
            - Urine sodium concentration
              - ≤ 30 mmol/l
                - Consider
                  - Diuretics or kidney disease?
                  - If ECF expanded consider
                    - Primary polydipsia
                    - Low solute intake
                    - Beer potomania
                  - If ECF reduced consider
                    - Vomiting
                    - Primary adrenal insufficiency
                    - Renal salt wasting
                    - Cerebral salt wasting
                    - Occult diuretics
              - > 30 mmol/l
                - Consider
                  - Diuretics
                  - Kidney disease
                  - All other causes

attention should be taken to avoid errors when calculating the required amount of sodium chloride. Administration of hypertonic saline should be done in environments where strict clinical and biochemical supervision can be undertaken.

Rate of correction of sodium is of utmost importance and the recommended rate of increase in serum sodium concentration is of a total of 10mmol/L during the first 24 hours and an additional 8mmol/L per day thereafter until sodium concentration reaches 130mmol/L. More rapid correction of serum sodium may lead to osmotic demyelination syndrome (ODS). This is a neurological disease caused by severe damage to the myelin sheath of nerve cells in the brain, which has serious neurological sequelae. Patients who are at increased risk of developing ODS include, alcohol abusers, patients with liver disease, use of thiazides or antidepressant medication, serum sodium <105mmol/L and hypokalaemia. In such patients, special caution should be taken in correcting their hyponatraemia.

**Chronic hyponatraemia**
In this scenario, the focus should be on trying to identify and treat the precipitating factor, rather than treating the hyponatraemia per se.

**Chronic hyponatraemia with reduced extracellular fluid volume**
In these scenarios, intravenous infusion of 0.9% sodium chloride or any crystalloid should be infused and cause-specific treatment started (Figure 1). In patients with haemodynamic instability, the need for rapid intravenous fluid resuscitation may override the risk of an overly rapid increase in sodium concentration. Cause specific treatment should be initiated as soon as the precipitating factor is identified.

**Chronic hyponatraemia with normal extracellular fluid volume**

**Syndrome of inappropriate antidiuresis (SIAD)**
Syndrome of inappropriate antidiuresis is a syndrome in which production of AVP is independent of the stimuli described above. (Figure 1) It results either from an increased release by the pituitary, or an ectopic source or from an increased sensitivity of the collecting duct to vasopressin. Table 1 defines the diagnostic criteria for diagnosing SIAD. Common causes for SIAD include:

- Malignancies especially lung and gastrointestinal;
- Pulmonary diseases;
- Central nervous system associated diseases;
- Drugs (Table 2);
- Idiopathic.

Treatment includes fluid restriction as first line. Other options for treatment include high solute intake with urea but this should be combined with sweet-tasting substances to mask the bitter taste of urea. Other treatment options include vasopressin receptor antagonists (vaptans) and Demeclocycline.

In the United States’, vaptan use may be considered in select circumstances, namely, an inability to tolerate fluid restriction or predicted failure of fluid restriction. In normal physiological states, AVP binds to V2 receptors in the collecting duct and an intracellular cascade is activated, resulting in the collecting duct being more permeable to water, thus retaining more water. Vaptans bind to these V2 receptors, blocking the action of AVP, thus rendering the collecting duct less permeable to water. This leads to an increased urine output which is solute-sparing, in contrast to loop diuretics which block sodium transporters, leading to simultaneous electrolyte and water loss. For this reason, the vaptans have been termed aquaretics.

In one systematic review, vaptans were found to increase serum sodium concentration modestly, but there was no

<table>
<thead>
<tr>
<th>Table 2: Drugs associated with SIAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric drugs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vasopressin analogues</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1: Criteria for diagnosis SIAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osmolality &lt;270m0sm/kg</td>
</tr>
<tr>
<td>Inappropriate urine osmolality &gt;100m0sm/kg</td>
</tr>
<tr>
<td>Renal sodium &gt;30mmol/l</td>
</tr>
<tr>
<td>Euvolaemia</td>
</tr>
<tr>
<td>Normal renal, adrenal, and thyroid function</td>
</tr>
</tbody>
</table>
significant reduction in risk of death\textsuperscript{12}. Also the risk of rapid increase in sodium was 2.5 times higher than when treated with placebo (relative risk 2.52, 95% CI 1.26-5.06). However there were no reports of osmotic demyelination syndrome. Tolvaptan, one of the vaptans, was studied in patients with autosomal dominant polycystic kidney disease\textsuperscript{13} and the tolvapan treatment group was noted to have an elevation of alanine aminotransferase greater than three times the upper limit of normal. But doses administered in these patients were higher than those used in hyponatraemia.

Demeclocycline is a tetracycline derivative and it causes a form of nephrogenic diabetes insipidus, irrespective of the serum AVP level\textsuperscript{14}. Treatment must be continued for several days to achieve maximal diuretic effect and dose should not be increased before 3-4 days have passed. Side effects of this drug include azotaemia, photosensitive skin rash and sometimes nephrotoxicity, especially in patients with cirrhosis. Therefore, renal function should be monitored on a regular basis.

**Chronic hyponatraemia with expanded extracellular fluid volume**

In these conditions, diuretic therapy and dietary sodium restriction form the mainstay of therapy\textsuperscript{2}. Fluid restriction may compliment this. Vaptans may be used in a subset of patients in whom hyponatraemia is limiting diuretic use or in whom there are mild symptoms thought to be due to hyponatraemia\textsuperscript{2}. The European Guidelines are more cautious in the use of vaptans, and in fact recommend against their use (See Figure 1) \textsuperscript{1}.

### Key points

- Hyponatraemia is associated with a wide range of non-specific clinical symptoms and even if chronic and seemingly asymptomatic, it may be associated with increased morbidity.
- Acute symptomatic hyponatraemia, especially with a serum sodium of less than 125mmol/l, should be managed promptly and under close supervision.
- 3% hypertonic saline may be used in such patients with great care, both in preparation and administration.
- Vaptans may be useful in a selected proportion of patients.

**Conclusion**

Treatment of acute hyponatraemia can be life-saving in some circumstances, although care should be taken to avoid correcting hyponatraemia too rapidly. Vaptan use may become a cornerstone in the treatment of hyponatraemia in the near future, although more data regarding its safety is awaited.

**Reference:**