Management of Electrolyte Imbalance due to Sodium
Evidence based review

Written for the College of Emergency Medicine e-learning programme in collaboration with Doctors.net.uk
Context

There are three compartments within the body containing water. These are the extracellular compartment, divided into the intravascular and interstitial spaces, and the intracellular compartment. (Figure 1)

Sodium is predominantly an extracellular cation and controls the movement of water between the intracellular and extracellular compartments. The movement of water is controlled by the sodium gradient between compartments. Normally, sodium leaks passively into cells and is transported back out of the cells by the Na⁺–K⁺ ATPase pump. When the extracellular sodium concentration rises, water will move out of the intracellular compartment into the extracellular space to maintain osmotic equilibrium. Water homeostasis and sodium regulation are controlled by thirst, the renin angiotensin system and antidiuretic hormone (ADH) or arginine vasopressin (AVP) in the kidneys. (Figure 2)

Figure 1. Water distribution in a 75 kg adult
Normal plasma osmolality is tightly controlled by these mechanisms and kept within a normal range of 275–295 mosm/l. The normal kidney can excrete between 400 ml and 10 l of water per day, thus protecting against hyper or hyponatraemia. When the control systems fail or the patient loses their ability to control their intake (for example very young infants, and elderly patients, particularly those in care), potential problems arise.

(i) Hyponatraemia

Definition

Hyponatraemia is defined as a serum Na⁺ ≤ 135 mmol/l. It has a reported incidence in clinical practice of between 15 and 30%.

Causes and classification

The causes of hyponatraemia (see Table 1) are classified according to the patient’s fluid status (euvolaemic, hypovolaemic, or hypervolaemic). Pseudohyponatraemia exists when there is a falsely low sodium measurement due to excessive lipids or protein in the plasma, or due to hyperglycaemia.
(where the movement of free water occurs into the extracellular space in response to the accumulation of extracellular glucose) (Biswas and Davies, 2007).

This classification system highlights the importance of assessing fluid status. For example, a patient with the syndrome of inappropriate antidiuretic hormone (SIADH) must be euvoalaemic, whereas a patient with cerebral salt wasting can have an identical picture to SIADH (low serum sodium, high urinary sodium with inappropriately concentrated urine) except the patient will be hypovolaemic. The causes of SIADH are listed in Table 2.

Hypovolaemic hyponatraemia is perhaps most commonly seen in the ED, and results from the loss of both water and sodium, but relatively more sodium.

There are three main causes of hypervolaemic hyponatraemia: congestive cardiac failure (CCF), renal failure and liver cirrhosis. In these cases total body sodium is increased but total body water is disproportionately greater leading to hyponatraemia and oedema.

In CCF reduced cardiac output leads to a fall in renal blood flow, stimulating ADH production and water resorption in the collecting ducts. The reduction in renal blood flow also stimulates the rennin-angiotensin system, leading to sodium and water retention. Hyponatraemia in CCF may also be exacerbated by diuretic use. It has been shown in a number of studies that hyponatraemia in CCF is a poor prognostic factor (Clayton and Le Jeune et al, 2006).

In liver cirrhosis several factors lead to hyponatraemia. These include reduction in circulating volume, portal hypertension leading to ascites, and failure of the liver to metabolise vasodilating substances. These changes result in stimulation of the rennin-angiotensin system and retention of sodium and water, but with relatively more water.

Ecstasy has hit the headlines due to deaths associated with its use. Hyponatraemia develops due to excessive water consumption and relatively lower sodium excretion (as in marathon runners) but other mechanisms described in the literature include increased ADH release, and reduced intestinal motility (Hall and Henry, 2006).

<table>
<thead>
<tr>
<th>Euvolaemic</th>
<th>Hypovolaemic</th>
<th>Hypervolaemic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH</td>
<td>GIT loss: Diarrhoea and vomiting</td>
<td>CCF</td>
<td>Hyperglycaemia Mannitol</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Bowel obstruction</td>
<td>Liver cirrhosis</td>
<td>administration</td>
</tr>
<tr>
<td>polydipsia</td>
<td>GI sepsis</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Renal loss:</td>
<td>Addison’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal tubular</td>
<td>Renal tubular acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td>Salt wasting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic use</td>
<td>Nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral salt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wasting</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Classification of hyponatraemia
Clinical presentation

The symptoms and signs of hyponatraemia can be very subtle and non-specific (see Table 3). It is important to establish whether the hyponatraemia is acute (developed in ≤ 48 hours) or chronic (developed in ≥ 48 hours). Much lower levels of sodium are tolerated if hyponatraemia develops chronically.

The aetiology of the hyponatraemia should be considered when taking the history and examining the patient, for example head injury, neurosurgery, abdominal symptoms and signs, pigmented skin (associated with Addison’s disease), drug history, etc. The patient’s fluid status is vitally important to diagnosis and subsequent management.

Table 3. Clinical features of hyponatraemia

Investigations

Firstly, confirm that the hyponatraemia fits with the clinical picture: sampling errors are not uncommon (e.g. when venepuncture is performed proximal to an intravenous infusion or is taken from an already established line). If in doubt repeat the sample.

Initial laboratory investigations should include glucose, plasma sodium, plasma osmolality, renal and liver function, plus urinary sodium and urine osmolality. Various combinations of the clinically assessed volume status and the urinary sodium concentration in patients with hyponatraemia are presented in Table 4. In patients who are more seriously ill, an arterial blood gas will be appropriate. Other tests to diagnose the cause may be required such as thyroid function, lipids, and adrenal function.

The osmolar gap should be calculated; it will help to detect any hidden osmoles such as mannitol, alcohol or ethylene glycol. A raised osmolar gap can also be seen in chronic renal failure, alcoholic...
and diabetic ketoacidosis, and lactic acidosis. The osmolar gap is the difference between the measured and the calculated osmolality: the calculated osmolality = 2(Na + K) + glucose + urea. A normal gap is 10–15 mmol/l.

<table>
<thead>
<tr>
<th><strong>Volume status</strong></th>
<th><strong>Urinary sodium</strong></th>
<th><strong>Likely diagnosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td>Low ≤ 10 mmol/l</td>
<td>Extrarenal sodium loss e.g. GIT loss, burns, fluid sequestration (peritonitis, pancreatitis)</td>
</tr>
<tr>
<td></td>
<td>High ≥ 20 mmol/l</td>
<td>Renal salt wasting e.g. salt losing nephropathy, hypothyroidism, adrenal insufficiency</td>
</tr>
<tr>
<td>Hypervolaemia</td>
<td>Low ≤ 10 mmol/l</td>
<td>CCF, liver cirrhosis, nephrotic syndrome (sodium retention due to poor renal perfusion – see text)</td>
</tr>
<tr>
<td>Euvolaemia</td>
<td>High ≥ 40 mmol/l</td>
<td>SIADH</td>
</tr>
</tbody>
</table>

Table 4. Typical combinations of results

**Treatment**

**HYONATRAEMIA**

1. Exclude pseudohyponatraemia
2. Calculate osmolar gap - 2hidden osmotes
3. Exclude artefactual cause (venepuncture proximal to iv infusion)

**ACUTE <48 HOURS**

- Symptomatic? e.g seizures or coma
- YES: Treat aggressively with hypertonic saline (3%), until sodium >120mmol/l
- NO: Aim to correct Na+ at the rate it declined - using normal saline or fluid restrict if appropriate

**CHRONIC >48 HOURS**

- If patient is shocked, resuscitate with normal saline
- SEEK EXPERT HELP
- AIM TO TREAT THE CAUSE
- HYPOVOLAEIC: Continue with normal saline until patient able to drink
- EUVOLAEIC: Fluid restrict to 500ml/24 hrs
- HYPERVOLAEIC: Fluid restrict and consider diuretics (not thiazides)
- Consider a Vasopressin Receptor Antagonist e.g. Tolvaptan

Figure 3. Management of hyponatraemia

Treatment of hyponatraemia should be guided by its chronicity, the patient’s fluid balance, and the potential aetiology.

In acute hyponatraemia (≤ 48 hours’ duration), prompt treatment and correction of the sodium is advised to prevent cerebral oedema. This is in contrast to chronic hyponatraemia, where correction
should be slow to prevent central pontine myelinolysis leading to permanent neurological damage. The target should be to raise the sodium to safe levels rather than to normalise it (≥ 120 mmol/l). The sodium should not reach normal levels within the first 48 hours.

Central pontine myelinolysis is a condition where focal demyelination occurs in the pons and extrapontine areas. This leads to serious and irreversible neurological sequelae which tend to be seen one to three days after the sodium has been corrected.

In patients with acute hyponatraemia and neurological sequelae (seizures or coma) treatment can be commenced with 3% saline (Androgue and Madias, 2000). There is no universal consensus to its use or the regime with which it should be administered: it can be started at 1–2 ml/kg/hr with regular measurements of serum sodium, urine output and cardiovascular status. It is recommended that the sodium be corrected by no more than 8 mmol in 24 hours (Androgue and Madias, 2000). Furosemide can also be used to remove free water.

There are various formulae used to calculate the volume of fluid and sodium to be administered. One example is the Androgue Madias formula, but there are variations on this which can also be used (Barsaum and Levine, 2002). The formula anticipates the change in serum sodium following the administration of one litre of a sodium containing infusion:

\[
\text{Change in Na}^+ \text{ mmol/l} = \frac{(\text{Na}^+ \text{ in infusate} - \text{serum Na}^+)}{\text{Total body water}^* + 1}
\]

* Total body water is estimated by weight and is roughly 0.5 x female weight, and 0.6 x male weight

**Example:**

A 60 kg female with serum sodium of 115 mmol:

(a) Using normal saline (contains 154 mmol/l of sodium):

\[
\text{Change in sodium} = 
\frac{154 \text{ mmol} - 115}{(0.5 \times 60)} + 1
\]

\[
= \frac{39}{31}
\]

\[
= 1.3
\]

Therefore 1 l of 0.9% (normal) saline will increase the serum sodium by 1.3 mmol.

(b) Using 3% saline (contains 514 mmol/l of sodium):

\[
\text{Change in sodium} = 
\frac{514 - 115}{(0.5 \times 60)} + 1
\]

\[
= \frac{399}{31}
\]

\[
= 12.9
\]

Therefore, 1 l of 3% saline will increase the serum sodium by 12.9 mmol.

Addison’s disease-associated hypovolaemic hyponatraemia should be treated with isotonic saline and urgent hormone replacement with hydrocortisone. These patients can require large volumes of fluid replacement when they are in crisis.

Chronic hyponatraemia can be treated by removing the cause (e.g. diuretics) and fluid restriction to around 500 to 800 ml/day. Vasopressin receptor antagonists are a new group of drugs for the treatment of hyponatraemia. They work by blocking the binding of ADH (AVP – arginine vasopressin)
in the distal nephron, therefore promoting the excretion of free water. Tolvaptan is one such drug and has been shown to effectively raise serum sodium in chronic euvoalaemic or hypervolaemic hyponatraemia (Schrier et al., 2006).

(ii) Hypernatraemia

Hypernatraemia is defined as serum sodium of greater than 145 mmol/ l and is always associated with a hyperosmolar state.

There is a significant morbidity and mortality associated with hypernatraemia which is hard to quantify due to its association with other serious co-morbidities. Some studies have quoted mortality rates as high as 75% (eMedicine, 2007).

Hypernatraemia leads to cell dehydration which causes cells to shrink. The cells respond by transporting electrolytes across the cell membrane and altering the resting membrane potential. About an hour later if hypernatraemia still exists, intracellular organic solutes are formed to restore cell volume and prevent structural damage. Therefore when replacing water it must be done very slowly to allow the accumulated solute to disperse and avoid cerebral oedema (eMedicine, 2007).

If hypernatraemia persists and the cells begin to shrink, cerebral haemorrhage can occur due to stretch and rupture of bridging veins (subdural, subarachnoid or intracerebral).

Causes and classification

The causes of hypernatraemia can be divided into three broad categories as shown in Table 5. It often has an iatrogenic cause and those most at risk are intubated patients, infants on formula milk, or the elderly and those in care who do not have fluids available to them or have an impairment of their thirst receptors.

<table>
<thead>
<tr>
<th>Reduced water intake</th>
<th>Loss of free water</th>
<th>Sodium gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unwell infants e.g. with diarrhoea and vomiting</td>
<td>1. Extra-renal: Dehydration Burns Exposure Gastrointestinal losses</td>
<td>Primary hyperaldosteronism (Conn’s)</td>
</tr>
<tr>
<td>Intubated patients</td>
<td>2. Renal: Osmotic diuretics e.g. Glucose, urea, mannitol Diabetes Insipidus (see table 6)</td>
<td>Secondary hyperaldosteronism e.g. CCF, liver cirrhosis, renal failure, nephrotic syndrome Iatrogenic – Sodium bicarbonate administration; hypertonic saline administration</td>
</tr>
<tr>
<td>Institutionalised elderly</td>
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</tbody>
</table>

Table 5. Causes of hypernatraemia

Diabetes insipidus is a condition characterised by abnormal ADH production (central) or ADH resistance (nephrogenic). There are many causes (see Table 6). The result is large volumes of very dilute urine (urine osmolality ≤ 150 mmol/ l) with a high serum sodium and osmolality.
Clinical presentation

The clinical features of hypernatraemia are non specific such as anorexia, nausea, vomiting, fatigue and irritability. As the sodium rises there will be alterations in neurological function which are more prominent if the sodium has risen rapidly and to high levels. Infants tend to develop tachypnoea, muscle weakness, restlessness, a high-pitched cry, and lethargy leading to coma. The main differential diagnosis for these symptoms in this population is sepsis which can itself be complicated by hypernatraemia.

Investigations

Investigations should follow a similar approach to hyponatraemia with a calculation of the osmolar gap, urinary sodium and osmolality along with further investigations to identify an underlying cause.

With renal causes of water loss, the urine osmolality will be very low, whereas in extra-renal causes, the urine osmolality will be very high (≥ 400 mosm/l), as the kidneys try to conserve water.

<table>
<thead>
<tr>
<th>Central</th>
<th>Nephrogenic</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
<td>Congenital renal disorders</td>
<td>Lithium</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Obstructive uropathy</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Tumours</td>
<td>Polycystic disease</td>
<td>Amphotericin</td>
</tr>
<tr>
<td>CNS infection: meningitis</td>
<td></td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>encephalitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Causes of diabetes insipidus
Treatment

Management consists of treating the underlying cause and correcting the hypertonicity. As with hyponatraemia, the general rule is to correct the sodium level at the rate at which it rose. If the sodium is corrected too rapidly there is a risk of developing cerebral oedema. Good advice is to aim for 0.5 mmol/l hour and a maximum of 10 mmol/l day in all except the very acute onsets.

In acute hypernatraemia (≤ 48 hours) the sodium can be corrected rapidly without causing problems. However, if there is any doubt as to the rate of onset, the sodium should be corrected slowly over at least 48 hours.

Patients with diabetes insipidus (DI) can normally manage their own fluid balance if they have free access to oral fluids. Patients with central DI may require treatment with desmopressin (i.e. replacement of ADH) but this should be guided by an endocrinologist.