Guidelines for the management of hyponatraemia in hospitalised patients

Authors: V Mishra

Aims: To provide guidelines for appropriate investigations and treatment of hyponatraemia in hospitalised patients.

<table>
<thead>
<tr>
<th>Normal range</th>
<th>Mild hyponatraemia</th>
<th>Moderate hyponatraemia</th>
<th>Severe hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>135-146 mmol/L</td>
<td>130-135 mmol/L</td>
<td>120-129 mmol/L</td>
<td>&lt;120 mmol/L</td>
</tr>
</tbody>
</table>

Evaluation of hyponatraemia

STEP 1: Rule out artefactual causes

- Is the patient on IV fluids?
- If so, could the sample have been taken “downstream” from the infusion site?
- Could the sample have been taken from the same line?

STEP 2: Clinical history

- Check fluid balance to exclude fluid overload
- Is the patient diabetic? Hyperglycemia may cause dilutional hyponatraemia and increased urinary loss of sodium
- Correct serum sodium for hyperglycemia (rise in plasma glucose >5.5mmol/L) by using equation given in (Appendix 1)
- Consider medications (Table 1). In some cases, stopping the medication or changing to an alternative that does not cause hyponatraemia may be sufficient. Monitor sodium concentrations to assess the effects of this management. It may take several days for the sodium to normalise after withdrawing medications
- Review clinical history for relevant conditions (such as congestive cardiac failure, kidney disease, liver failure, lung pathology)
- Loss of weight/appetite: investigate for malignancy
Table 1: Drugs known to cause hyponatraemia

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Examples known to cause hyponatraemia (other compounds may exist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Bendroflumethiazide, Metolazone, Indapamide, Chlortalidone</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Furosemide, Bumetanide, Torasemide</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Amiloride, Spironolactone, Triamterene, Eplerenone</td>
</tr>
<tr>
<td>Combined diuretics</td>
<td>Co-amilofruse, Co-amiloxide</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Tricyclic (&amp; related) antidepressants</td>
<td>Amitriptyline, Clomipramine, Dosulepin, Imipramine, Nortriptyline, Trimipramine, Mianserin, Trazodone</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Phentazine, Isocarboxazid, Tranilcypramine, Moclobemide</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, Valproate</td>
</tr>
<tr>
<td>Others</td>
<td>Venlafaxine, Duloxetine, Chlorpropamide, Glimepiride, Glipizide</td>
</tr>
</tbody>
</table>

STEP 3: Clinical examination to assess extracellular volume (Appendix 2)

- Hypovolaemia: Signs of dehydration, such as hypotension, tachycardia, oliguria, dry oral mucosa, reduced skin turgor, reduced central venous pressure
- Euvolaemia: Normal blood pressure, pulse rate, central venous pressure
- Hypervolaemia: Pedal oedema/ascites

Clinical findings must be considered when requesting and interpreting the results of laboratory investigations

STEP 4: Biochemical investigation

Samples should be sent to the laboratory for the following investigations as soon as possible, and preferably before starting treatment:

- Paired serum and spot urine for U&E and osmolality
- Plasma glucose

If there is suspicion of adrenal insufficiency or severe hypothyroidism, the following investigations should be performed:

- 9 am serum for cortisol; if equivocal, a short synacthen test may be necessary
- Thyroid function tests

Hyponatraemia may be categorised into three types, depending on the extracellular fluid volume and biochemical investigations.

When requesting tests through ICE (RLBUHT), click on the “Hyponatraemia investigations” link for a list of tests that should be requested to investigate a patient with hyponatraemia

When requesting tests through Medway (AUH), request blood biochemistry(U&E, TFT, cortisol, glucose, osmolality) and urine (U&E and osmolality)
Figure 1: Flowchart to aid in diagnosis of underlying causes of hyponatraemia

Exclude artefactual causes

Check medications
Is patient on medications listed in Table 1?

Check fluid balance
Is patient in positive fluid balance?

Send hyponatraemia investigations (ICE/MEDWAY)

Assess patient’s volume status clinically

Hypovolaemia

Renal or extra-renal loss of sodium

Euvolaemia

Urine sodium >30mmol/L

Medications (Table 1)
Glucocorticoid deficiency
Severe Hypothyroidism
SIADH

Hypervolaemia

Acute kidney injury
Chronic kidney disease
Congestive cardiac disease
Liver cirrhosis
Nephrotic syndrome

Discontinue IV fluids, start fluid restriction
Monitor serum sodium for 2 to 3 days

Discontinue medications
Monitor serum sodium for 2 to 3 days
Management of hyponatraemia

**Treatment depends on the patient’s**
- Estimated volume status
- Serum sodium concentration
- Chronicity
- Rate of fall of the serum sodium concentration

**Hypovolaemic hyponatraemia**
- Rehydrate with sodium chloride 0.9% infusion or balanced crystalloid solution (Hartmann)
- Volume and rate of fluid to be administered in severe chronic hyponatraemia can be calculated by equation 1 (see below)
- Hartmann (balanced crystalloid solution) should be preferred over normal saline provided patient does not have hyperkalaemia, alkalosis (raised bicarbonate) and hypercalcaemia
- Normal saline should be given where there is upper gastrointestinal loss (loss of hydrochloride) or serum chloride <98 mmol/L
- Check U&E after infusion and prescribe further fluids based upon the result

**Hypervolaemic hyponatraemia**
- Fluid and salt restriction
- Consider diuretics
- Treat the underlying cause

**Euvolaemic hyponatraemia**
- If possible treat the cause (e.g. chest infection, malignancy or hormonal insufficiency)
- If treating SIADH (Appendix 3) - Commence fluid restriction (500-750 ml/day)
- Maintain accurate fluid balance chart
- Measure weight of the patient daily
- If serum Na not corrected despite adherence to appropriate fluid restriction, consider Tolvaptan
  *(only after discussion with Endocrinology consultant)*
Management of Severe Symptomatic Hyponatremia (Serum Na <120mmol/L)

Patient with severe hyponatraemia presenting with symptoms as shown in Table 2

Table 2: Clinical presentation in severe symptomatic hyponatraemia

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately severe</td>
<td>Nausea without vomiting</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Severe</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Cardiorespiratory distress</td>
</tr>
<tr>
<td></td>
<td>Abnormal and deep somnolence</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Coma (Glasgow Coma Scale ≤ 8)</td>
</tr>
</tbody>
</table>

Management of severe symptomatic hyponatraemia (Table 2)

Patient should be managed in ITU/HDU under close supervision and monitoring

- 90mls of 5% saline IV (through central line) over 20 min
- Continue the same dose every 20 min
- Stop the infusion if either happens first
  - serum Na increases by 5 mmol/L
  - clinical improvement in symptoms
- Recheck serum Na after every infusion dose

Clinical Improvement after increase in serum Na by 5 mmol/L (calculation 1)

- Start with normal saline (0.9%) at rate so that serum Na increases by 0.5 mmol/L/hour. Overall increase in serum Na should be
  - 10 mmol/L during the first 24 hours
  - additional 8 mmol/L for every 24 hours or 18 mmol/L in 48 hours
- Continue till serum Na reaches 130 mmol/L

No clinical Improvement after increase in serum Na by 5 mmol/L (calculation 2)

- Continue with 5% saline with rate of increase in serum Na 1 mmol/L/hour
- Stop the infusion if either happens first:
  - improvement in clinical symptoms
  - total increase in serum Na by 10 mmol/L
  - Serum Na reaches 130 mmol/L
- Keep checking serum sodium every 4 hourly
*If symptoms do not improve by increasing the serum Na by 10mmol/L or serum Na reaches 130mmol/L; investigate for any other cause responsible for symptoms other than hyponatremia.

Management of moderately symptomatic hyponatraemia (Table 2)

**Patient can be managed on ward as follows**

- 250mls of 1.8% saline IV (through peripheral line) over 20 min
- Continue the same dose every 20 min
- Stop the infusion if either happens first
  - serum Na increases by 5 mmol/L
  - clinical improvement in symptoms
- Recheck serum Na after every infusion dose

**Clinical Improvement after increase in serum Na by 5 mmol/L (calculation 1)**

- Start with normal saline (0.9%) at a rate 0.5 mmol/L/hour so that increase in serum Na
  - 10mmol/L during the first 24 hours
  - additional 8mmol/L for every 24 hours or 18mmol/L in 48 hours
- Continue till serum Na reaches 130mmol/L

Please contact the Duty Biochemist in Clinical Biochemistry or On call Endocrinology SpR (through the switch board) for advice on management of hyponatremia.
APPENDICES

Appendix 1
Equation for correction of serum sodium for hyperglycaemia

Corrected serum Sodium (mmol/L) =

Measured serum sodium + 2.4 \times \frac{[\text{Serum Glucose (mmol/L)} - 5.5\text{mmol/L}]}{5.5\text{mmol/L}}

Adapted from Hillier et al (1999)

Appendix 2  Classification of Hyponatraemia

Hypovolaemic hyponatraemia

- Whole body sodium and water depletion, with renal or extra-renal sodium loss
- Extra-renal loss of sodium stimulates the renin-angiotensin-aldosterone axis, reducing the excretion of sodium in the urine (urine Na ≤30 mmol/L)
- In cases of renal loss (including diuretics), there is increased excretion of sodium (urine Na >30 mmol/L)
- Clinically these patients present with signs and symptoms of dehydration

Hypervolaemic hyponatraemia

- An excess of sodium and a greater excess of water
- Accumulation of interstitial fluid reduces the effective circulating volume, which stimulates aldosterone and ADH secretion, increasing the reabsorption of sodium and water from the kidney
- Clinically may present with detectable oedema or ascites due to reduced oncotic pressure, which causes a shift of fluid into the interstitial space

Euvolaemic hyponatraemia

- Normal whole body sodium with water excess
- The cause of apparently euvolaemic hyponatraemia is often not immediately apparent
- In hospitalised patients, a common cause of euvolaemic hyponatraemia is inappropriate intravenous fluids
- Other causes of euvolaemic hyponatraemia must be ruled out before the diagnosis of SIADH is made (see Appendix 2). SIADH should be differentiated from cerebral salt wasting syndrome (see Appendix 2)
Appendix 3  Criteria for the diagnosis of SIADH

Criteria for the diagnosis of SIADH

- Serum osmolality <275mosm/kg
- Urine osmolality >100mosm/kg
- Urine sodium >30mmol/L
- Absence of adrenal, thyroid, pituitary or renal insufficiency
- Clinically euvoalaemic

Adapted from Schwartz et al(1997)

Appendix 4

Management of severe hyponatraemia

(serum sodium <120mmol/L)

Definition

- Acute hyponatremia is defined as hyponatremia (serum Na < 135mmol/L) presenting within 48 hours
- Symptomatic hyponatremia is defined as any biochemical degree of hyponatremia presenting with moderately to severe neurological symptoms
- Symptomatic hyponatremia is usually associated with acute severe hyponatremia at serum Na < 120mmol/L

Pathogenesis of Symptomatic hyponatremia

- When hyponatremia develops within few hours(<48hours), ability of brain cells to adapt is exceeded and results in cerebral oedema(low osmolality)
- It is usually seen in post operative conditions associated with excess fluid retention
- It is a life threatening condition as it can result in severe brain damage or death of the patient
- After 48 hours (chronic hyponatremia) brain cells adapt by extruding sodium, potassium, chloride and osmolytes and return to their normal size (normal osmolality). Therefore patients with chronic hyponatremia are asymptomatic

Clinical presentation of symptomatic hyponatremia

- The symptoms of acute severe hyponatremia is due to cerebral oedema leading to brain herniation which is life threatening
- A small increase in serum Na rapidly by 5mmol/L is effective as it increases the osmolality, reduces brain swelling and intracerebral pressure
  - Infusion of hypertonic saline increases the serum Na rapidly and is effective in patients with symptomatic hyponatremia

Na content :

- 0.9% saline = 154mmol/1000mls
- 1.8% saline= 308mmol/1000mls
- 5% saline= 856mmol/1000mls

Total body water:

- Non-elderly men: 0.6
- Non-elderly women: 0.5
- Elderly men: 0.5
- Elderly women: 0.45
Calculations (Adrogue-Madias, NEJM 2000;342:1581-1589)

To achieve serum Na at 0.5 mmol/L/hour with normal saline (Calculation 1)
The following formula can be used to calculate Na replacement using 0.9% saline
- In order to achieve a 0.5 mmol/h increase in serum Na, use this formula to calculate the amount of intravenous sodium needed per hour (mmol/h):
  - Amount of sodium replacement (mmol/h) = 0.6(total body water in non-elderly man) x
    weight (kg) x 0.5 (desired correction rate mmol/h)
  - When using 0.9% saline (Normal Saline)(1000ml contains 154 mmol sodium) the rate of infusion required to achieve a 0.5 mmol/h improvement in serum sodium is given by:

\[
\text{Amount of sodium replacement (mmol/h)} \times \left(\frac{1000}{154}\right) = \text{ml/hr of 0.9% saline required}
\]

For Example: for an 80 kg patient
- 0.6 x 80 x 0.5 = 24 mmol/hr sodium required
- 24 X\left(\frac{1000}{154}\right) = 156\text{ml/hr of 0.9% saline}

To achieve serum Na at 1 mmol/L/hour with hypertonic saline (Calculation 2)
The following formula can be used to calculate sodium replacement using 1.8% or 5% saline
- In order to achieve a 1 mmol/h increase in serum Na, use this formula to calculate the amount of intravenous Na needed per hour (mmol/h):
  - Amount of sodium replacement (mmol/h) = 0.6(total body water in non-elderly man) x
    weight (kg) x 1 (desired correction rate mmol/h)
  - When using 1.8% saline(1000ml contains 308 mmol Na) the rate of infusion required to achieve a 1 mmol/h improvement in serum Na is given by:

\[
\text{Amount of sodium replacement (mmol/h)} \times \left(\frac{1000}{308}\right) = \text{ml/hr of 1.8% saline required}
\]

For Example: for an 80 kg patient:
- 0.6 x 80 x 1 = 48 mmol/hr sodium required
- 48 X\left(\frac{1000}{308}\right) = 155\text{ml/hr of 1.8% saline}
<table>
<thead>
<tr>
<th>Acute severe symptomatic hyponatraemia</th>
<th>Chronic severe hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration: &lt;48 hours</td>
<td>Duration: ≥48 hours</td>
</tr>
<tr>
<td>Morbidity: Brain herniation</td>
<td>Morbidity: Osmotic demyelination syndrome</td>
</tr>
<tr>
<td>Neurological symptoms are present: Seizures, confusion, headache, low GCS, coma</td>
<td>Neurological symptoms are absent</td>
</tr>
<tr>
<td>Commonly seen in post-operative patients, patients with self-induced water intoxication associated with endurance exercise, psychiatric diseases (eg, acute psychosis, schizophrenia), use of drugs such as “ecstasy” (methyleneoxy-N-methamphetamine or MDMA)</td>
<td>Can be seen with any type of hyponatraemia:</td>
</tr>
<tr>
<td>○ Urgent correction by 4-6 mmol/L to prevent brain herniation and neurological damage from cerebral ischemia</td>
<td>○ Rate of correction should be between 10-12 mmol per 24 hours</td>
</tr>
<tr>
<td>○ Severe symptoms: 100 mL of 3% saline infused intravenously over 10 minutes X 3 as needed</td>
<td>○ In high risk patients should be 8 mmol per 24 hours</td>
</tr>
<tr>
<td>○ Mild to moderate symptoms with a low risk of herniation: 3% saline infused at 0.5-2 mL/kg/h</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Verbalis J (2013) et al

**References**
