Hyponatraemia

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation. Please answer True or False:

Regarding hyponatraemia:

a. Hyponatremia is an independent risk factor for increased mortality
b. 99% of the sodium filtered by the kidney is reabsorbed in the distal tubule
c. Malnourished patients and alcoholics are at increased risk of osmotic demyelination
d. A urinary sodium level below 20 mmol/l is suggestive of an extra renal cause of hypovolaemic hyponatremia
e. Disorientation, weakness and confusion are typically seen in chronically hyponatremic patients with sodium levels between 130-125 mmol/l

SUMMARY

• Sodium disorders are the most common electrolyte abnormalities seen in hospitals.
• Hyponatraemia is often iatrogenic in in-patients and severe sodium disturbances are associated with considerable morbidity and mortality. Disorders of sodium balance can be confusing.
• Categorisation based on fluid status aids diagnosis of the underlying cause and helps guide treatment.
• The speed with which hyponatremia develops is important as it both influences presenting symptoms and dictates initial management. In acute cases there is a greater risk of cerebral oedema and rapid correction is beneficial, especially in the presence of coma or convulsions.
• Rapid correction can be dangerous, however, in patients with chronic hyponatremia as osmotic demyelination is a greater risk in these patients. Here slower, careful correction of sodium is usually indicated and serum sodium should not be increased by more than 4-8 mmol/l/day

INTRODUCTION

The presence of hyponatremia has been demonstrated to be an independent risk factor for increased mortality in hospital inpatients. As hyponatremia is the most common electrolyte disturbance encountered in clinical medicine, it is vital that doctors and nurses know how to appropriately manage this condition. Severe hyponatremia has long been recognised to be associated with adverse outcomes. It is also increasingly being recognised that even mild hyponatremia can be associated with patient harm, with even relatively minor derangements having been shown to be associated with increased falls and fractures.

Appropriate management of hyponatremia is often challenging due to both numerous pathophysiological mechanisms and multiple underlying pathological conditions. After revising the normal control of sodium balance this article will review the causes, classification, diagnosis and management of hyponatremia. An algorithm for investigations and treatment is provided at the end of this article.

CONTROL OF SODIUM BALANCE

Sodium is the most prevalent cation in the extracellular fluid (ECF). Total body sodium is therefore proportional to ECF volume. Under normal circumstances serum sodium levels are maintained within a tight physiological range of between 135-145mmol/l. Despite great variation in the intake of both sodium and water, close control of serum sodium is
Euvolaemic hyponatremia is the most common category of hyponatremia seen in hospital in-patients. SIADH is the most common cause of euvolaemic hyponatremia and it is associated with many different disorders. These can be divided into several major etiologic groups but this is beyond the scope of this article. If SIADH is suspected it can be useful to measure urine osmolality as a urine osmolality >100 mOsm/kg in the presence of hyponatraemia reflects inappropriate anti-diuresis. As SIADH remains a diagnosis of exclusion other potential causes must be investigated and excluded first.
Table 1: Table showing some important causes of SIADH with examples of major groups of causes and descriptions of specific causes.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Commonly thiazide diuretics, vincristine and cyclophosphamide. Many others including SSRIs, sodium valproate and haloperidol. For a more comprehensive list see Binu et al, 2011.</td>
</tr>
<tr>
<td>CNS disorders</td>
<td>Infection, trauma, ischemia, haemorrhage and psychosis can increase the release of ADH.</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Commonly of the lung, particularly small cell carcinoma. Other tumours can less frequently have a similar effect. These include head and neck, duodenal and pancreatic cancers.</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Pneumonia, asthma and acute respiratory failure have been known to cause SIADH.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Major surgery can lead to increased secretion of ADH.</td>
</tr>
<tr>
<td>Nephrogenic SIADH</td>
<td>Due to aV2 receptor gene gain of function mutation. This leads to excess water reabsorption in the renal collecting duct.</td>
</tr>
<tr>
<td>Infective</td>
<td>Acquired immune deficiency syndrome.</td>
</tr>
</tbody>
</table>

CNS= central nervous system. SIADH= Syndrome of inappropriate anti-diuretic hormone secretion. SSRI= selective serotonin reuptake inhibitor.

Other common causes of euvolaemic hyponatremia include:
- Glucocorticoid deficiency - cortisol deficiency may lead to failure of ADH suppression
- Hypothyroidism- hyponatremia secondary to hypothyroidism is rare. It is thought to result from impaired water excretion due to decreased glomerular filtration rate (GFR) secondary to the systemic effects of thyroid hormone deficiency on peripheral vascular resistance and cardiac output
- Low Solute Intake- e.g. beer potomania where the primary abnormality is not one of water balance but sodium balance due to reduced intake
- In the vast majority of cases excessive water intake in isolation is insufficient to overwhelm the capacity of the kidneys to excrete water. Therefore severe hyponatremia due to excess water intake alone is rare in the presence of normal renal function. If water intake exceeds 20 l/day, as seen in psychogenic polydipsia, it is possible to achieve a transient hyponatremia, but in the absence of other dysfunction this is rapidly corrected on cessation of fluid intake. It is more likely that patients with high fluid intakes and accompanying hyponatremia have a concurrent impairment of water excretion which has previously gone unnoticed during periods of normal water ingestion. In patients with known psychiatric disorders who consume large volumes of water this is often a result of iatrogenic SIADH, for example as a side effect of selective serotonin reuptake inhibitors. Acute psychosis has also been shown to increase ADH secretion

Hypervolaemic hyponatremia
This is a situation characterised by a paradoxical increase in total body sodium, but a simultaneous and proportionally larger increase in total body water leading to a dilutional hyponatremia. This reduction in water excretion is secondary to either an excess of ADH secretion or an element of renal impairment limiting the maximal excretion of free water. Underlying pathologies include nephrotic syndrome, congestive cardiac failure (CCF) and cirrhosis (although rarely in the absence of ascites). In all of these situations there is oedema secondary to impairment of the kidney’s ability to excrete water maximally. This results from either inappropriate ADH secretion leading to water retention or an inappropriate distribution of fluid within the body, preventing intravascular fluid elimination.

Hyponatraemia without hypo-osmolality
As stated previously, hyponatraemia and hypo-osmolality almost always co-exist and this is referred to as “true hyponatremia.” Hyponatremia occurring without hypo-osmolality is referred to as pseudohyponatremia. Pseudohyponatremia can occur with a normal or elevated serum osmolality. Pseudohyponatremia with normal serum osmolality occurs when grossly elevated levels of lipids or proteins lead to an artificial apparent decrease in measured
The algorithm below provides a useful structure for investigating and managing hyponatremia.

INVESTIGATION

The diagnosis of underlying cause is difficult and should be carried out with the help of an endocrinologist. A careful history with particular reference to the patient’s recent medications and fluid intake should be taken. A clinical examination, looking for indicators of volume status, e.g. oedema, jugular venous pressure; signs of adrenocortical insufficiency including pigmentation, postural hypotension; stigmata of hypothyroidism; or any signs related to chest or central nervous system disease, in particular underlying neoplasia, should be carried out.

Assessment of volaemic status using clinical examination is notoriously unreliable, however and must be made in conjunction with the history and blood and urine tests.

Radiological investigations where indicated might include CT of brain, thorax, abdomen and pelvis.

Urine osmolality and electrolytes, thyroid function tests, random cortisol and/or short synacthen test, lipids, and serum electrophoresis are required.

The algorithm below provides a useful structure for investigating and managing hyponatremia.
MANAGEMENT

General advice

Because there are inherent risks associated with both hyponatraemia and its rapid correction, appropriate management of hyponatraemia involves balancing these risks. Patients, who have developed a sodium imbalance over a longer period of time are likely to have made appropriate compensatory changes. They are therefore better able to tolerate severe hyponatraemia. Additionally in these patients slow correction is much safer as discussed later. In contrast, in patients who have developed hyponatraemia over a short timeframe, a faster resolution may be appropriate, particularly if there are signs of neurological compromise.

The major risk associated with excessively rapid sodium correction is osmotic demyelination. This can result in severe and permanent neurological impairment or death. Certain patient groups such as the malnourished, alcoholics, those with burns and those with hypokalemia are at increased risk of osmotic demyelination. Osmotic demyelination occurs as a result of the failure of the adaptations that prevent chronically hyponatraemic patients from developing cerebral oedema. Over-rapid correction in these patients prevents the brain from replacing organic osmoles at an appropriate speed. The resultant osmotic stress leads to osmotic demyelination. This condition has previously been known as central pontine myelinolysis, due to its tendency to affect the pons, which has a dense concentration of heavily myelinated ascending and descending tracts which are particularly vulnerable to osmotic stress. However these changes have been reported in extra-pontine sites also. The key features of osmotic demyelination are shown below. While it is known that resolution of hyponatraemia should be tailored to the speed of the acquisition of the imbalance, there is no clear consensus on the absolute safe rate, and it may be that none exists.

Over-rapid correction is extremely common, despite the use of formulae to guide sodium correction. This is because volume repletion, irrespective of the fluid’s actual sodium content, can switch off ADH production and cause a rapid rise in sodium level.

Importantly, there are case reports of successful treatment of osmotic demyelination treated by acutely reloowing the serum sodium with dextrose and/ or desmopressin in cases of overshoot correction, thereby buying time for organic osmoles to recumulate.
Osmotic demyelination

- Presentation is usually delayed by 2-5 days following correction
- Diagnosis may be very difficult in sedated and ventilated patients
- Clinical features are varied, including bulbar problems, paraplegia, quadriplegia and locked-in syndrome
- Changes are often irreversible but re-lowering of serum sodium has anecdotal efficacy in the event of overly rapid correction.
- Where indicated, MRI is the imaging modality of choice.

Management of acute hyponatremia

Recommendations for the rate of correction of acute hyponatremia are based on avoiding brain herniation, something that is almost exclusively seen in acute hyponatremia. These patients have the greatest risk of cerebral oedema but a lower risk of demyelination when compared with chronically hyponatraemic patients. Therefore prompt partial correction of hyponatremia is indicated. Limited available literature suggests that an increase in serum sodium of 4-6 mmol/l or to exceed the seizure threshold of 120 mmol/l is adequate to reverse the most severe manifestations of acute hyponatremia.

In acute hyponatremia severe neurological symptoms may be treated with a 100 ml bolus of 3% hypertonic saline. This can be given intravenously over 10 minutes. This bolus may be repeated twice if severe neurological symptoms persist. The aim of this emergency treatment is to address neurological complications such as cerebral oedema, hyponatremic seizures or reduced level of consciousness. Importantly the aim is not to return serum sodium levels to within the normal range. In acute hyponatremia once symptoms have resolved, it becomes less important to rapidly correct the sodium level, and in these instances an increase in serum sodium rates of up to 2 mmol/l/hour may be appropriate.

If hypertonic saline (3% sodium chloride) is used in acute symptomatic patients, specialist advice should be sought. Very close (1-2 hourly) monitoring of plasma sodium should be performed. These patients should be admitted to a critical care unit, if such facilities are available. Some authors advocate the use of a loop diuretic in combination with hypertonic saline in order to enhance free water clearance, however extreme caution is required as this may lead to too rapid a rise in sodium.

Management of chronic hyponatremia

It is widely accepted that patients with chronic hyponatremia are susceptible to adverse neurological outcomes when sodium levels are rapidly corrected due to iatrogenic brain damage. Current guidance suggests the desired increase in serum sodium in chronic hyponatremia should be 4-8 mmol/l/day for those at low risk of osmotic demyelination syndrome. In patient groups where the risk of osmotic demyelination syndrome is high, it has been suggested that an even lower goal of 4-6 mmol/l/day be targeted. For patients with severe symptoms, the entire 6mmol/l can be achieved during the first 6 hours of therapy, with subsequent treatment delayed until the next day. Sterns et al. have described a rule of sixes that some may find helpful: six a day makes sense for safety; so six in six hours for severe symptoms and stop.

As the precise time course of the disturbance is often not clear it is often safer to adopt slow correction for all patients unless adverse neurological symptoms and signs mandate a more rapid correction or there is absolute certainty about the time course. Specific tips for the management of the different subtypes of true hyponatremia are given below.

Hypovolaemic hyponatremia

In hypovolaemic hyponatremia, the aim is to correct the volume deficit, as the relative water excess will correct itself via a water diuresis once circulating volume is restored. Fluids such as 0.9% should be administered until blood pressure is restored and the patient has clinical euvolemia. Hypovolaemic hyponatremia is almost always an example of chronic hyponatremia, so slow correction should be employed.

Euvolaemic hyponatremia

In euvoalaemic hyponatremia, as with all hyponatremia, management is dictated by the underlying cause, the chronicity or acuteness of the imbalance and the presence or absence of neurological symptoms. Water restriction of 1-1.5 l/day may be used. Drugs that may have caused SIADH should be discontinued and any underlying causes addressed.

Hypervolaemic hyponatremia

In hypervolaemic hyponatremia, fluid restriction is the mainstay of treatment. Strict restriction is often necessary to achieve a negative solute-free water balance. Typical initial fluid restriction for a normal sized adult should be around 1-1.5 litres per day. Loop diuretics are sometimes used to remove excess fluid with urine usually hypotonic to plasma.
CONCLUSION

Hyponatremia is a condition associated with significant morbidity and mortality. Treatment is guided by the underlying cause, speed of onset and the presence of adverse neurological signs. In the absence of severe neurological signs, current guidance suggests that correction of serum sodium should not exceed 4-8 mmol/l/day in patients with chronic hyponatremia. Lower rates of correction may be indicated in patients with chronic hyponatremia who have additional risk factors for osmotic demyelination. More rapid correction should only be targeted in cases where there is certainty that the hyponatremia is acute or if the hyponatremia is causing severe neurological symptoms. Too rapid correction of hyponatremia may risk permanent severe neurological damage or death.

Answers to questions

a) True. It is associated with increased mortality along with prolonged hospital stays and increased falls.

b) False. Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. The proportion of sodium reabsorbed in the distal tubule is much smaller but exerts the most influence on total sodium balance.

c) True. Patients with advanced liver disease are also at increased risk.

d) True. It is often gastrointestinal in origin.

e) False. Such signs are usually only seen when serum sodium levels reach 115-120 mmol/l.

References


