Hyponatraemia

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Summary

- Sodium disorders are the most common electrolyte abnormalities seen in hospitals.
- Hyponatraemia is often iatrogenic in inpatients, 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 hyponatraemia develops is important. In acute cases there is a greater risk of cerebral oedema and rapid correction is beneficial.
- However, rapid correction can be dangerous in patients with chronic hyponatraemia.

INTRODUCTION

The presence of hyponatraemia has been demonstrated to be an independent risk factor for increased mortality in hospital inpatients.[1] As hyponatraemia is the most common electrolyte disturbance encountered in clinical medicine,[1] it is vital that doctors and nurses know how to appropriately manage this condition. Severe hyponatraemia has long been recognised to be associated with adverse outcomes.[2] It is also increasingly being recognised that even mild hyponatraemia can be associated with patient harm, with even relatively minor derangements having been shown to be associated with an increased risk of falls and fractures.[3–5]

Appropriate management of hyponatraemia is often challenging because of both numerous pathophysiological mechanisms and multiple underlying pathological conditions.[6] After revising the normal control of sodium balance this article will review the causes, classification, diagnosis and management of hyponatraemia. 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 and 145 mmol L^{-1}. Despite great variation in the intake of both sodium and water, close control of serum sodium is maintained via control of the excretion of water and sodium.[7] Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. This reabsorption occurs at a relatively fixed rate, regardless of total body sodium. It is the smaller proportion of sodium, reabsorbed in the distal tubule and collecting ducts, that exert the most influence on total sodium balance,[8] but serum sodium levels reflect water balance under the influence of antidiuretic hormone (ADH).

THE ROLE OF ANTIDIURETIC HORMONE

The majority of hyponatraemic states involve inappropriately elevated levels of ADH.[9] This causes disproportionate retention of water compared with sodium. The secretion of ADH is influenced by multiple factors such as plasma osmolality and circulating volume. Failure to suppress ADH production in lowered osmolality states is a feature of SIADH (syndrome of inappropriate ADH secretion). By contrast, continued production of ADH despite a lowered serum osmolality is a feature of oedema-forming conditions such as heart failure and liver

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disease.[10] In these conditions ADH production continues because reduced renal perfusion causes excess aldosterone production.

CAUSES OF HYPONATRAEMIA

True hyponatraemia
As sodium and its accompanying anions are the major effective plasma solutes in the ECF, hyponatraemia and hypo-osmolality almost always coexist. True hyponatraemia is regarded as a low sodium level in the presence of hypo-osmolality.

The situations in which hyponatraemia can occur without hypo-osmolality are discussed later.

True hyponatraemia is characterised by hypo-osmolality. This is because sodium in the ECF and potassium in the intracellular fluid (ICF) (along with their associated anions) determine osmolality, with water moving freely between fluid compartments, in order to maintain the same osmolality between compartments. As a result, plasma hypo-osmolality, and therefore hypotonic hyponatraemia, indicates a relative excess of water to sodium regardless of volume status.

It is an oversimplification to regard hypo-osmolar states as produced by either water excess or solute depletion as often components of both are involved.[11] It can be useful though to classify hyponatraemia on the basis of fluid status. This can facilitate understanding of the processes involved in the development of hyponatraemia and also help guide management.

Categorisation into one of three clearly defined groups based on volume status is not always possible due to multiple aetiologies and patient co-morbidities. However, inappropriate categorisation of hyponatraemia and subsequent mismanagement has been shown to lead to poor clinical outcomes,[12] whilst following a simple algorithm for the diagnosis and treatment of hyponatraemia has been shown to be associated with improved outcomes.[13]

Hypovolaemic hyponatraemia
In hypovolaemic hyponatraemia total body water and total body sodium are both low, but there is disproportionate loss of sodium compared with water. This is a result of the increased ADH secretion seen in hypovolaemic states causing increased water reabsorption. Hyponatraemia is often compounded by thirsty patients consuming hypotonic fluids at a level inadequate to try to restore circulating volume.

Sodium loss can be renal or extrarenal, and establishing the urinary sodium level is important in distinguishing between the two. A urinary sodium level below $20\,mmol\,L^{-1}$ is suggestive of an extrarenal cause.[12,14] Extrarenal causes are commonly of gastrointestinal origin. Other causes include exercise-associated hyponatraemia (also commonly seen in people working in hot conditions), burns, trauma and

pancreatitis. Renal causes include diuretic excess, renal failure, salt-wasting nephropathy, aldosterone deficiency, chronic pyelonephritis, nephrocalcinosis, proximal renal tubular acidosis and ketonuria.[12]

Euvolaemic hyponatraemia
Euvolaemic hyponatraemia is the most common category of hyponatraemia seen in hospital inpatients.[12] SIADH is the most common cause of euvolaemic hyponatraemia and is associated with many different disorders. These can be divided into several major aetiological groups, but a discussion of these this is beyond the scope of this article.

If SIADH is suspected, it can be useful to measure urine osmolality as a urine osmolality $> 100\,mosm\,kg^{-1}$ in the presence of hyponatraemia reflects inappropriate antidiuresis. As SIADH remains a diagnosis of exclusion other potential causes must be investigated and excluded first.

Other common causes of euvolaemic hyponatraemia include:

- Glucocorticoid deficiency – cortisol deficiency may lead to failure of ADH suppression.
- Hypothyroidism – hyponatraemia 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 – here the primary abnormality is one not of water balance but of 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 hyponatraemia due to excess water intake alone is rare in the presence of normal renal function. If water intake exceeds 20 litres per day, as seen in psychogenic polydipsia, it is possible to achieve a transient hyponatraemia, but in the absence of other dysfunction this is rapidly corrected on cessation of fluid intake.[12] It is more likely that patients with high fluid intakes and accompanying hyponatraemia have a concurrent impairment of water excretion that 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 hyponatraemia
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 hyponatraemia. 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.

Table 1. *Some important causes of SIADH with examples of major groups of causes and descriptions of specific causes*

Cause	Description
Drugs	Commonly thiazide diuretics, vincristine and cyclophosphamide. Many others including selective serotonin reuptake inhibitors, sodium valproate and haloperidol. For a more comprehensive list, see Binu et al.[15]
Central nervous system disorders	Infection, trauma, ischaemia, haemorrhage and psychosis can increase the release of ADH[16,17]
Malignancies	Commonly of the lung, particularly small cell carcinoma.[18] Other tumours can less frequently have a similar effect. These include head and neck, duodenal and pancreatic cancers[15,19]
Pulmonary disease	Pneumonia, asthma and acute respiratory failure have been known to cause SIADH[15]
Surgery	Major surgery can lead to increased secretion of ADH.[20,21] This is thought to involve a pain afferent-mediated response
Nephrogenic SIADH	Due to a vasopressin receptor 2 (VR2) gene gain-of-function mutation. This leads to excess water reabsorption in the renal collecting duct[22]
Infective	Acquired immune deficiency syndrome[23,24]
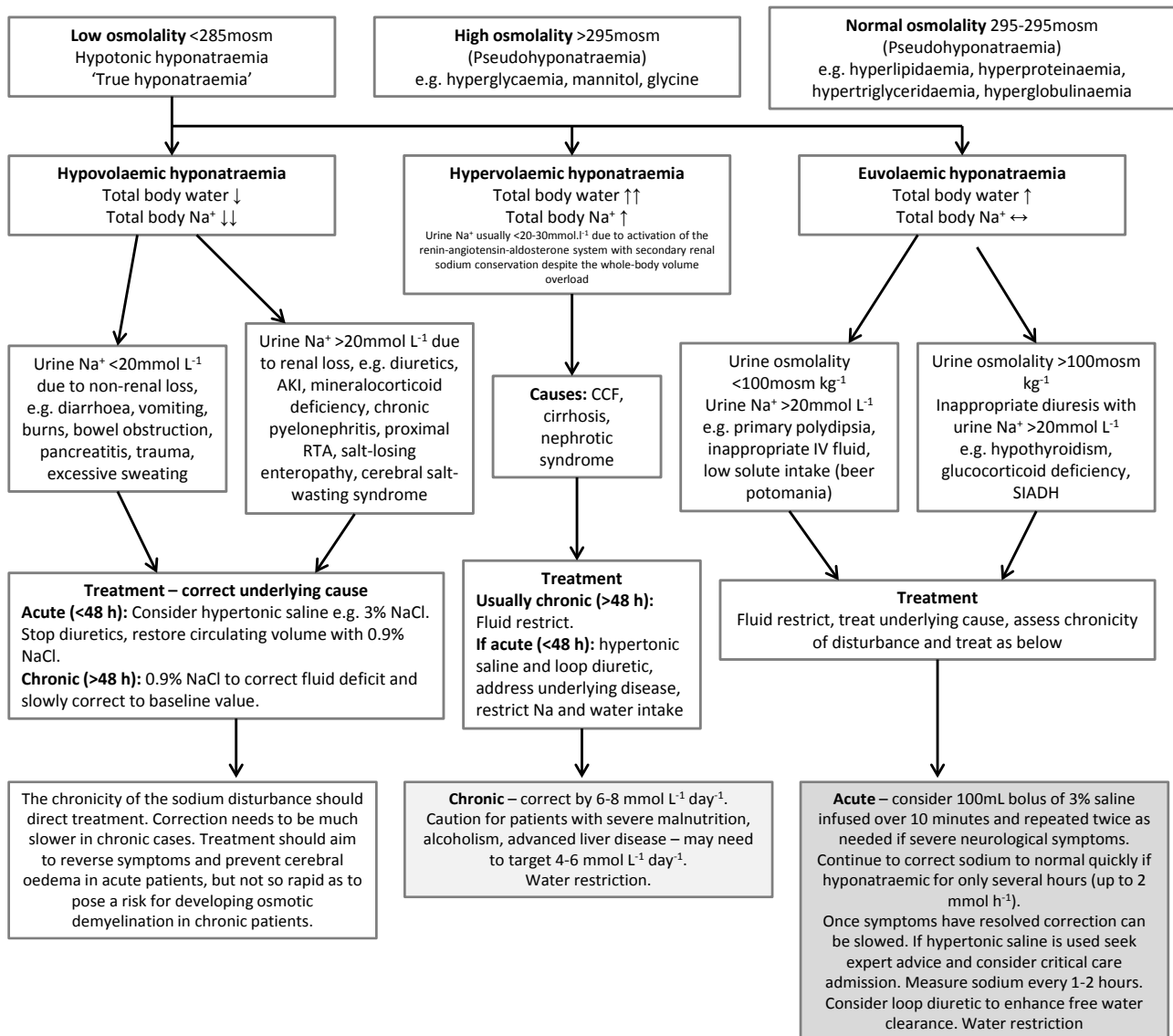
Figure 1. *Hyponatraemia treatment algorithm*

Underlying pathologies include nephrotic syndrome, congestive cardiac failure and cirrhosis (although rarely in the absence of ascites).[10] 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 coexist, and this is referred to as 'true hyponatraemia'. Hyponatraemia occurring without hypo-osmolality is referred to as pseudohyponatraemia. Pseudohyponatraemia can occur with a normal or elevated serum osmolality. Pseudohyponatraemia with normal serum osmolality occurs when grossly elevated levels of lipids or proteins lead to an artificial apparent decrease in measured a serum sodium. This is because sodium normally distributes in the aqueous phase of plasma, which accounts for 93% of the plasma volume. A correction factor for whole plasma can be rendered incorrect if the non-aqueous phase is increased due to hypertriglyceridaemia or paraproteinaemia.[17]

The use in laboratories of direct ion-sensitive electrodes eliminates this potential error. Hypertonic hyponatraemia refers to hyponatraemia with an increased osmolality. This occurs when sodium and its associated anions are no longer the major effective solutes present in the plasma. This 'translocation hyponatraemia' is the due to osmotically active solutes in the plasma which are unable to cross the cell membrane. While many solutes, such as urea and ethanol, can enter cells and so cause hypertonicity without cell dehydration, other molecules, such as glycine, cannot. Glucose normally diffuses freely into cells but when insulin is deficient, such as in diabetic ketoacidosis (DKA), glucose is effectively confined to the ECF. When the concentration of glucose rises, water is displaced across the membrane from inside to outside the cell. As well as dehydrating the cell, this leads to a dilutional hyponatraemia. In DKA, the 'true' corrected serum sodium can be estimated from the formula:

$$[Na^+] \text{ corrected} = [Na^+] \text{ measured} + \{(\text{glucose} - 5.6) \times 0.288\}$$

It is an important axiom of treatment of DKA, especially in children, that the corrected sodium concentration should rise slowly as glucose falls, to avoid the risk of cerebral oedema secondary to plasma hypo-osmolality.

SYMPTOMS AND SIGNS OF HYPONATRAEMIA

The symptoms and signs associated with hyponatraemia relate to both the degree of imbalance and the time course over which the imbalance has developed. Neurological symptoms can occur as a result of an osmotic gradient between the ICF ECF compartments. This gradient causes water to move into cells, resulting in tissue oedema.[27,28] This process is clinically most important in the brain as, due to the exhaustion of adaptive mechanisms and confinements

of the skull, cell swelling here can lead to raised intracranial pressure and neurological damage. This situation occurs most often when hyponatraemia develops over a short time frame.

If severe hyponatraemia develops over the course of hours or a few days, rather than over many days or weeks, then the ability of the brain to adapt to osmotic changes and cell swelling is more rapidly exceeded. This leads to the development of cerebral oedema.[29] Patients in whom acute severe hyponatraemia has developed in under 48 hours can present with alarming neurological findings such as coma and convulsions. Additionally they are at risk of death as a result of cerebral herniation.[30]

Rapidly evolving severe hyponatraemia is a different disease entity from slowly evolving hyponatraemia. Brain adaptation seen in slowly evolving hyponatraemia may prevent cerebral oedema. This occurs via the transport of sodium, chloride and potassium to the ECF. This compensatory mechanism maintains ICF osmolality equal to equal ECF osmolality and thereby avoids large shifts of water into the cells.[31] Over a period of time organic solutes such as glutamine, glutamate and taurine follow into the ECF to maintain this osmotic stability. These molecules are known as 'organic osmolytes'.

The clinical result of this compensation is that these patients experience fewer and less severe symptoms and generally do not die as a result of brain herniation.[31] Slowly evolving hyponatraemia is frequently asymptomatic, but there are limits to how low levels can get before physiological processes are affected, regardless of the chronicity of the process.[12] Non-specific symptoms generally develop when serum sodium levels drop below 120 mmol L^{-1}. These symptoms include fatigue, lethargy, weakness and confusion. Seizures and coma are uncommon. As well as time frame, symptoms are also dependent on the patient's premorbid state. Certain groups, such as children, hypoxic patients and premenopausal women, are at increased risk of cerebral oedema.[32]

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 computed tomography of brain, thorax, abdomen and pelvis. Measurement of

urine osmolality and electrolytes, thyroid function tests, a random cortisol and/or short Synacthen test, blood lipid profile and serum electrophoresis are required.

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

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.[31] They are therefore better able to tolerate severe hyponatraemia. Furthermore, 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.[33] 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 hypokalaemia, are at increased risk of osmotic demyelination.[12]

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 osmolytes at an appropriate speed. The resultant osmotic stress leads to osmotic demyelination.[33,34] 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 that are particularly vulnerable to osmotic stress. However, these changes have been reported in extrapontine sites also.[35] The key features of osmotic demyelination are described 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 re-lowering the serum sodium with dextrose and/or desmopressin in cases of overshoot correction, thereby buying time for organic osmolytes to recumulate.[36]

Management of acute hyponatraemia

Recommendations for the rate of correction of acute hyponatraemia are based on avoiding brain herniation, something that is almost exclusively seen in acute hyponatraemia.[12,37,38] These patients have the greatest risk of cerebral oedema but a lower risk of demyelination than chronically hyponatraemic patients. Therefore. prompt partial correction of hyponatraemia is indicated. The limited literature available suggests that an increase in serum sodium of 4–6 mmol L^{-1} or to exceed the seizure threshold of 120 mmol L^{-1} is adequate to reverse the most severe manifestations of acute hyponatraemia.[38]

In acute hyponatraemia severe neurological symptoms may be treated with a 100 mL bolus of 3% hypertonic saline.[32,39] This can be given intravenously over 10 minutes. This bolus may be repeated twice if severe neurological symptoms persist.[12] The aim of this emergency treatment is to address neurological complications such as cerebral oedema, hyponatraemic seizures or reduced level of consciousness. Importantly, the aim is not to return serum sodium levels to within the normal range. In acute hyponatraemia, 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^{-1} h^{-1} may be appropriate.[40]

If hypertonic saline (3% sodium chloride) is used in acute symptomatic patients, specialist advice should be sought. Very close (1 to 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.[40]

Management of chronic hyponatraemia

It is widely accepted that patients with chronic hyponatraemia are susceptible to adverse neurological outcomes when sodium levels are rapidly corrected due to iatrogenic brain damage.[12,29,33,34,38,41–43] Current guidance suggests the desired increase in serum sodium in chronic hyponatraemia should be 4–8 mmol L^{-1} day^{-1} for those at low risk of osmotic demyelination syndrome.[12] 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^{-1} day^{-1} be targeted.[12] For patients with severe symptoms, the entire 6 mmol L^{-1} can be achieved during the first 6 hours of therapy, with subsequent treatment delayed until the next day. Sterns and Hix[44] have described a rule of sixes that some may find helpful: six a day makes sense for safety; so six in 6 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 hyponatraemia are given below.

Hypovolaemic hyponatraemia

In hypovolaemic hyponatraemia, 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 euvolaemia.[12] Hypovolaemic hyponatraemia is almost always an example of chronic hyponatraemia, so slow correction should be employed.

Euvolaemic hyponatraemia

In euvolaemic hyponatraemia, as with all hyponatraemia, 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 litres per day may be used. Drugs that may have caused SIADH should be discontinued and any underlying causes addressed.

Hypervolaemic hyponatraemia

In hypervolaemic hyponatraemia, 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.[12]

CONCLUSION

Hyponatraemia 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^{-1} day^{-1} in patients with chronic hyponatraemia. Lower rates of correction may be indicated in patients with chronic hyponatraemia who have additional risk factors for osmotic demyelination. More rapid correction should only be targeted in cases where there is certainty that the hyponatraemia is acute or if the hyponatraemia is causing severe neurological symptoms. Too rapid correction of hyponatraemia may risk permanent severe neurological damage or death.

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