The adult patient with hyponatraemia

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Revalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference
1A01, 2C01, 3C00

Key points

Sodium is the most abundant and osmotically important extracellular cation.

Disorders of sodium balance are common, and often multifactorial.

Assessment of hyponatraemic patients should include past medical and drug history, drinking habits, and volume status. Initial investigations should include paired (plasma and urine) osmolalities and urinary sodium. Management of sodium disorders requires restoration of normal sodium and water balance in a well-controlled monitored environment. Specific treatment depends on the cause.

Sodium should be increased by a maximum of 4–6 mmol per 24 h to reduce the risk of demyelinolysis.

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Sodium is the most abundant cation in extracellular fluid (ECF), accounting for 86% of plasma osmolality, and is therefore of major importance when considering the physiological effects of hyponatraemia.[1] Disorders of sodium balance (usually mild) can occur in up to 30% of inpatients,[2] and are associated with increased mortality and length of hospital stay. Hyponatraemia usually reflects an excess of body water relative to sodium, being classified as *hypervolaemic*, *hypovolaemic*, or *euvolaemic*. It has varying osmolar states and can become life-threatening if unrecognized or managed incorrectly because of a failure to appreciate changes in plasma osmolality and subsequent osmotic movement of water (below). This article describes sodium homeostasis, the pathophysiology of hyponatraemia, plus the assessment and management of hyponatraemia via clinical scenarios to illustrate educational and practical points.

Sodium homeostasis

Sodium in the ECF is normally maintained at 134–146 mmol litre^{-1}. Total body sodium content is 58 mmol kg^{-1} and daily requirement is 2 mmol kg^{-1}. *Osmolarity* is defined as the number of osmoles per litre of solution. *Osmolality* is the number of osmoles per kilogram of solvent and may be estimated by the following calculation: Osmolality=2 (Na+K) +Glucose+Urea (mOsm kg^{-1}) (all in mmol litre^{-1}).

From the above equation, it is evident that sodium is a major determinant of serum osmolality (normally maintained at 280–295 mOsm kg^{-1}). Neuroendocrine homeostatic mechanisms compensate for high or low sodium intake by altering its renal reabsorption. Such control is closely linked to patients' volaemic state, water homeostasis and maintenance of normal osmolality in the ECF. Increases in ECF osmolality as small as 1–2% stimulate the posterior pituitary gland to release vasopressin [also called antidiuretic hormone (ADH)]. Vasopressin acts on V2 receptors in the distal nephron to increase water reabsorption via aquaporin-2 channels. Thirst is also stimulated resulting in increased oral intake of water in the conscious patient. Any subsequent reduction in plasma osmolality suppresses ADH secretion.

Hypovolaemia stimulates increased renin secretion from the renal juxtaglomerular cells. Renin converts angiotensinogen into angiotensin I which, via angiotensin converting enzyme, is converted into angiotensin II, stimulating the adrenal cortex to release aldosterone. Reductions in plasma sodium detected in the renal cortex also stimulate aldosterone secretion; a mineralocorticoid that acts on the principle cells in nephron collecting ducts to increase sodium reabsorption and, via osmosis, water reabsorption. Aldosterone also causes sodium reabsorption from sweat, saliva, and the colon. Any subsequent increase in ECF volume inhibits aldosterone secretion via a negative feedback loop. Urine osmolality reflects these changes, varying between 50 and 1400 mOsm kg^{-1}.

Aetiology of hyponatraemia

Hyponatraemia can be classified as *mild* (130–135 mmol litre^{-1}), *moderate* (125–129 mmol litre^{-1}), or *severe* ($\leq$125 mmol litre^{-1}) and occurs via three basic mechanisms[2]:

(i) Gaining water in isolation: syndrome of inappropriate ADH (SIADH), dextrose infusion.
(ii) Gaining water to a greater extent than gaining sodium: liver failure, CCF, nephrotic syndrome.
(iii) Sodium depletion to a greater extent than that of water:
  (a) Renal: cerebral salt wasting syndrome, diuretics.
  (b) Non-renal: gastrointestinal losses, cutaneous losses (sweating) or so-called 'third space' losses (e.g. burns, pancreatitis, and trauma).

Mechanistic descriptions include *hypertonic* (dilutional), *isotonic* (pseudohyponatraemia), or

doi:10.1093/bjaceaccp/mku045
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Table 1 Causes of hyponatraemia

Classification	Examples
Hypotonic hypovolaemic	Diarrhoea, vomiting, sweating, burns, Addison's, pancreatitis, trauma, and cerebral salt wasting syndrome
Hypotonic euvolaemic	Syndrome of inappropriate ADH (SIADH), hypothyroidism, glucocorticoid insufficiency, hypotonic fluids, drugs (diuretics, PPIs, AEDs, antibiotics, and SSRIs)
Hypotonic hypervolaemic	Cirrhosis, heart failure, nephrotic syndrome, renal failure, and pregnancy
Isotonic pseudohyponatraemia	Hyperlipidaemia, hyperproteinaemia (multiple myeloma and recent immunoglobulin therapy)
Hypertonic dilutional	Severe hyperglycaemia, glycine, and mannitol

hypotonic (which may be hypervolaemic, euvolaemic, or hypovolaemic (Table 1).

Understanding the pathophysiology of each of these helps guide management, varying from fluid restriction to replacement of water and sodium losses. A well-monitored environment with frequent blood sampling is therefore necessary to effectively manage hyponatraemia.

The patient with hyponatraemia

Presentation

Frequently an incidental finding with non-specific symptoms (e.g. headache, nausea, vomiting, confusion, muscle cramps, or in severe cases seizures and coma). Symptoms are less common with serum sodium concentrations above 125 mmol litre^{-1}.

Assessment

Clinical and biochemical assessment of the patient are essential. This includes a full past medical history and drug history, as acute and chronic disease plus medications can cause hyponatraemia (Table 1). A history of patients' drinking habits should also be sought.

Examination should focus on the assessment of volume status including skin turgidity, tachycardia, postural hypotension, and evidence of oedema. Clinical signs of other disease processes that could cause hyponatraemia should be sought (Table 1).

Initial investigations include urea and electrolytes, paired serum and urine osmolalities, thyroid stimulating hormone (TSH), ACTH, cortisol, and urinary sodium. History or examination findings may indicate additional investigations (Table 2). Diagnostic algorithms can improve the accuracy of determining underlying aetiologies.[3] One example is: http://cdn.lifeinthefastlane.com/wp-content/uploads/2010/06/Hyponatraemia-Flow1.jpg.

Clinical scenarios

The following scenarios outline some common presentations of hyponatraemia. They aim to demonstrate the clinical features, typical investigations, and explain the pathophysiology and rationale for treatment in each patient.

Table 2 Investigations for hyponatraemia

For all patients:	*Consider:*
Serum and urine osmolalities	Short synacthen test
Urinary sodium	ECG
Blood glucose	Chest X-ray
TSH	Abdominal ultrasound
Cortisol	CT head, thorax, abdomen, pelvis
ACTH	Echocardiography
Urine dip (proteins and ketones)	

Clinical scenario 1

A previously well 30-year-old female presents with 5 days of diarrhoea. On examination: heart rate (HR): 120, blood pressure (BP): 90/50, cool peripheries, capillary refill time (CRT) 4 s. Blood tests show Na 130 mmol litre^{-1}, K 3.2 mmol litre^{-1}, urea 15 mmol litre^{-1}, and creatinine 127 μmol litre^{-1}. Plasma osmolality was 273 mOsm kg^{-1}, urine osmolality 380 mOsm kg^{-}1, and urinary Na $<$20 mmol litre^{-1}. TSH and cortisol concentrations were within normal limits.

This is *hypotonic hypovolaemic hyponatraemia*; urine osmolality is high and urinary sodium low because of the *normal physiological response* to dehydration and gastrointestinal sodium losses. A similar clinical and biochemical picture would occur in the case of excessive sweating (e.g. extreme sport, as there would again be renal reabsorption of sodium and water). Urinary sodium should be interpreted with caution; if this patient was taking diuretics urinary sodium may have been high. It is nevertheless important to exclude other pathologies (e.g. hypothyroidism) even if the patient appears to be purely gastrointestinal as the aetiology of hyponatraemia is commonly multifactorial.[4]

Management principles

The patient requires water and sodium replacement (normal saline supplemented with potassium) until euvolaemic. If medications were implicated [e.g. diuretics or proton pump inhibitors (PPIs)] stopping or substituting the drugs would form part of the management strategy.

Clinical scenario 2

A 65-year-old female smoker attends with cough, breathlessness and haemoptysis. On examination, she has clubbing of the fingers and is cachectic. HR: 80, BP: 140/80, CRT $<$2 s, normal jugular venous pressure, chest clear, and no peripheral oedema. Blood results: Na 109 mmol litre^{-1}, K 4.2 mmol litre^{-1}, urea 5.6 mmol litre^{-1}, and creatinine 63 μmol litre^{-1}. Serum osmolality was 263 mOsm kg^{-1}, urine osmolality 250 mOsm kg^{-1}, and urinary Na 42 mmol litre^{-1}.

This is an example of SIADH (Table 3), caused in this instance by bronchogenic carcinoma. SIADH causes hypotonic euvolaemic hyponatraemia because of an isolated increase in total body water. Normally excess water intake would result in urine osmolality of $<$100 mOsm kg^{-1}, but in SIADH there is inappropriate water retention because of excess ADH, so the urine concentration, and

therefore osmolality, is abnormally high. Criteria for diagnosing SIADH include: clinical euvolaemia, serum osmolality <275 mOsm kg^{-1}, urine osmolality >100 mOsm kg^{-1}, urinary Na >30 mmol litre^{-1}, normal thyroid/adrenal function, and no use of diuretics within a week of testing.[3]

Management principles

Seek an underlying cause and commence water restriction (1000 ml day^{-1}) although this is often poorly adhered to. *Demeclocycline* can be introduced in addition to water restriction if the sodium is not increasing. This is a tetracycline antibiotic known to cause nephrogenic diabetes insipidus by inhibiting the action of ADH in the nephron. If the serum sodium is failing to correct within 3 days of the above management, the V2 receptor antagonist *tolvaptan* (in association with ongoing fluid restriction) should be considered in consultation with a Consultant Endocrinologist to avoid 'over-rapid' correction of serum sodium.[5] Side-effects to be aware of include nausea, weakness, hyperkalaemia, and postural hypotension.

Cerebral salt wasting syndrome (CSWS) can be mistaken for SIADH as the biochemical picture is similar. Like SIADH it results in a hypotonic hyponatraemia, high urinary Na, and high urine osmolality. The distinguishing features are that in CSWS the patient is hypovolaemic, with polyuria (Table 4). It is rare and typically associated with recent intracranial surgery. The process is usually self-limiting and treated with isotonic saline.

Clinical scenario 3

A 65-year-old gentleman with a background of ischaemic heart disease and depression presents with breathlessness bibasal crepitations and ascites. Blood results: Na 106 mmol litre^{-1}, K 5.6 mmol litre^{-1}, urea 8.6 mmol litre^{-1}, and creatinine 153 μmol litre^{-1}. Serum osmolality 254 mOsm kg^{-1}, urine osmolality 304 mOsm kg^{-1}, and urinary Na 19 mmol litre^{-1}. Liver function, TSH, and cortisol were normal.

This is hypotonic hypervolaemic hyponatraemia. Because of congestive cardiac failure the patient has an ineffective circulating volume resulting in secondary hyperaldosteronism, causing increased sodium and water reabsorption. In normal individuals exposed to prolonged high concentrations of mineralocorticoids, the renal response to aldosterone decreases, preventing oedema and fluid overload. However in cirrhosis, nephrosis, and heart failure this so-called 'escape phenomenon' is reduced or absent.[6] This patient was also on fluoxetine, which may have contributed to the hyponatraemia.

Table 3 Causes of SIADH

	Examples
Intracranial	Trauma, tumour, meningitis, encephalitis, subarachnoid haemorrhage, CVA, post-surgical, and epilepsy
Pulmonary	Pneumonia (bacterial, viral, and fungal), TB, sarcoidosis, and abscess
Malignancy	Small cell lung cancer, mesothelioma, lymphoma, nasopharyngeal cancer, GI, or GU tract malignancy
Drugs/toxins	Desmopressin, PPIs, SSRIs, TCAs, haloperidol, carbamazepine, sodium valproate, levetiracetam, cyclophosphamide, oxytocin, and ecstasy
Miscellaneous	HIV, acute intermittent porphyria, and Guillain–Barré syndrome

Management principles

The primary problem is water excess and secondary problem sodium excess. Loop diuretics (e.g. furosemide increases water and sodium clearance and, if administered as an infusion, can limit the rate of sodium increase). His antidepressant therapy may also need to be changed if thought to be contributory.

Clinical scenario 4

A previously well 60-year-old gentleman becomes confused and breathless in recovery after a trans urethral resection of prostate (TURP). Arterial blood gas shows: Na 120 mmol litre^{-1}, K 3.4 mmol litre^{-1}, and a mild metabolic acidosis.

This is likely to be a case of TURP syndrome as a result of absorption of irrigation fluid used intraoperatively. Of note 1.5% glycine, a naturally occurring amino acid and inhibitory CNS transmitter, is commonly used as it has favourable optical and osmotic characteristics, and lacks allergic potential. Absorption of glycine initially causes transient dilutional hypervolaemic hypotonic hyponatraemia as a result of the hypotonic (200 mOsm kg^{-1}), salt-free solution. The unmetabolized proportion of glycine (10%) later causes a natriuresis and osmotic diuresis, resulting in a hypertonic hypovolaemic hyponaraemia. Symptoms of TURP syndrome are thought to be predominantly caused by the initial hypo-osmolar state, and by the dose-dependent CNS effects of glycine.[7] Ammonia, a metabolite of glycine, may also contribute as a cerebral

Table 4 Classification of hyponatraemia with examples

Classification of hyponatraemia	Total body water	Total body sodium	ECF volume	Examples
Hypotonic hypovolaemic	↓	↓↓	↓	Urinary Na <20 mmol litre^{-1}: Gastrointestinal losses, sweating, burns, trauma Urinary Na >40 mmol litre^{-1}: Addison's, cerebral salt wasting, diuretics
Hypotonic euvolaemic	↑	↔	↔/↑	Urinary Na <20 mmol litre^{-1}: Hypothyroidism, hypotonic fluids, primary polydipsia Urinary Na >40 mmol litre^{-1}: SIADH, glucocorticoid insufficiency, drugs
Hypotonic hypervolaemic	↑↑	↑	↑↑	Urinary Na <20 mmol litre^{-1}: CCF, liver failure, nephrotic syndrome Urinary Na >40 mmol litre^{-1}: renal failure
Isotonic pseudohyponatraemia	↔	↔	↔	Hyperlipidaemia, hyperproteinaemia
Hypertonic dilutional	↔	↔	↔	Hyperglycaemia, glycine, and mannitol

depressant. Measured osmolality is often higher than the calculated osmolality because of the unmeasured glycine, resulting in an increased osmolar gap.

Management principles

Patients with low sodium but normal osmolality are often asymptomatic, and require monitoring only. As the glycine metabolizes and is excreted the sodium will return to normal. Those patients who are hypo-osmolar or symptomatic need to be monitored in critical care environment, to maintain negative free water balance. Furosemide can be used to treat pulmonary oedema, but if causing further sodium loss then mannitol is a useful alternative. Sodium replacement with concomitant use of normal saline infusion may be required.

Pitfalls in sodium measurement

Routine laboratory sodium measurement uses a method called *indirect ion selective electrode* (ISE) sampling. High lipid or protein concentrations can interfere with this (e.g. high triglycerides or multiple myeloma) as the presence of the molecules dilute sodium in the serum sample causing a falsely low reading (i.e. *isotonic pseudohyponatraemia*). The use of a *direct ISE analyser* corrects for this. Severe hyperglycaemia (diabetic ketoacidosis, hyperosmolar non-ketotic acidosis) also affects concentrations of sodium. Osmotic diuresis can cause hypernatraemia, and hyperglycaemia can cause a hypertonic dilutional hyponatraemia as a result of the hyperosmolar environment caused by excess glucose. Tonicity describes the tendency to gain or lose water in a given environment. If cells are in a hypertonic environment, water moves from the intracellular space into the ECF. In a hypotonic environment the reverse occurs, causing cells to swell and, in severe cases, rupture their membranes. Freely permeable solutes do not affect tonicity as they can evenly distribute across cell membranes. However, impermeable solutes (glucose, mannitol, and glycine) can cause discrepancies in tonicity and subsequent osmosis in order to restore isotonic environments. In hyperglycaemia, the sodium concentrations are said to decrease by 1 mmol litre^{-1} for every 3.5 mmol litre^{-1} increase in glucose.[8] Therefore, as glucose is corrected, the sodium concentrations may increase rapidly and, for this reason, frequent monitoring is necessary. Even in severe hyperglycaemia the sodium concentrations are measured accurately by both direct and indirect ISE testing unless the sample is also hyperlipaemic (common in this population).

Rate of correction of hyponatraemia

Complications of hyponatraemia occur via two generic mechanisms

Biochemistry of hyponatraemia

Hyponatraemia and subsequent hypotonic ECF cause water to move into cells by osmosis. In the brain this leads to cerebral oedema and, if occurring rapidly (<48 h), the additional intracranial volume causes raised intracranial pressure with the potential for brainstem herniation in severe cases.

Management of hyponatraemia

Rapidly correcting chronic hyponatraemia increases the risk of myelinolysis through sudden increases in plasma osmolality. Water moves out of neurones into the ECF causing them to shrink, creating conditions for central, and extra pontine myelinolysis (Fig. 1).

Current recommendations are to control the increase of sodium to no more than 4–6 mmol litre^{-1} in 24 h, 12–14 mmol litre^{-1} in 48 h, and 14–16 mmol litre^{-1} in 72 h.[9] In moderate-to-severe cases, this requires blood sampling every 1–2 h and is therefore best managed in a critical care environment with an arterial line. There are many formulae available to calculate fluid requirements, though these should only be used as a guide as they make many assumptions including these calculated fluids being the sole sodium source for the patient.[9] Critical care patients often receive extra sodium as many infusions and antibiotics are made up in saline. A pharmacist can help identify which infusions can be made up in dextrose to reduce the sodium load. Normal saline is the fluid of choice in most cases, but Hartmann's solution may be used if there is hyperchloraemia. Three per cent of saline should be reserved for those patients with severe neurological compromise (seizures and coma).

If the rate of increase of sodium is faster than recommended, a peripheral dextrose infusion can be started. If the patient is

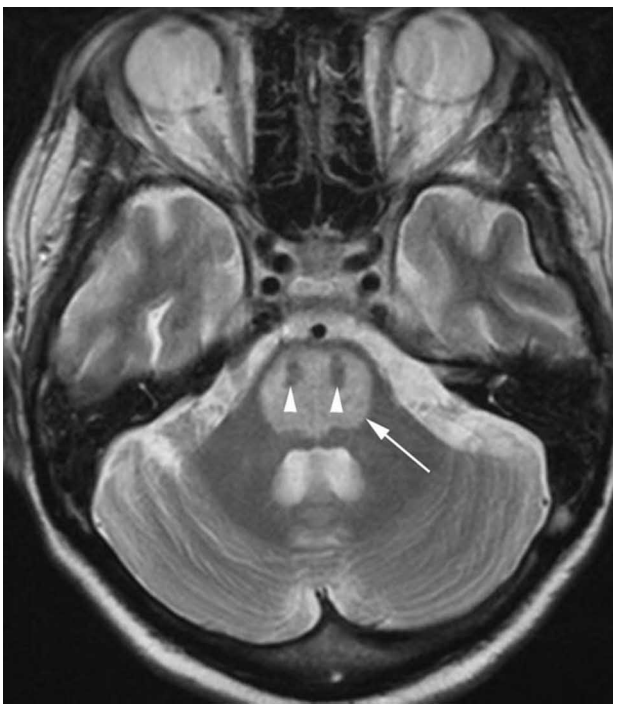

Fig 1 MRI image of central pontine myelinolysis. There is a high T2 signal in the centre of the pons (white arrow) with sparing of the corticospinal tracts (white arrow heads) (with thanks to Dr Charles Romanowski, Consultant Neuroradiologist, Royal Hallamshire Hospital).

concurrently requiring renal replacement therapy (e.g. continuous veno venous haemofiltration) an alternative strategy is to add sterile water to the replacement fluid, adjusting the sodium concentration of the bag to the required target.[10] This will result in lower concentrations of other electrolytes (potassium and bicarbonate) in the solution, which may require peripheral or enteral supplementation.

Conclusions

Hyponatraemia is the most commonly encountered electrolyte disorder. Diagnosis may be incidental (e.g. through before operation assessment) or may be the consequence of a symptomatic presentation. Understanding the pathophysiology of hyponatraemia aids assessment, investigation, and appropriate treatment strategies. In severe cases, patients are best monitored in a critical care environment with frequent blood sampling. An endocrinologist should be consulted to guide investigations and management. Acute hyponatraemia can cause cerebral oedema. Over-rapid correction of hyponatraemia risks myelinolysis; therefore, the rate of increase in sodium should be carefully controlled to no more than 4–6 mmol litre^{-1} per 24 h.

Declaration of interest

None declared.

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