



# Severe hyponatraemia – recognition and management

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## Summary

**Hyponatraemia is the most common electrolyte disorder. In its severe form it has a high morbidity and mortality. The cause of the hyponatraemia must be identified by clinical assessment and investigations including serum and urinary sodium and osmolality. Determining if the patient is euvolaemic, hypovolaemic or hypervolaemic helps guide treatment. Most cases are caused by drugs, inappropriate secretion of antidiuretic hormone, and fluid retaining conditions such as heart failure. In addition to managing the underlying cause, severe hyponatraemia requires correction of the serum sodium. Treatment should be in an intensive care unit. Correcting the serum sodium too quickly risks causing cerebral demyelination which is frequently fatal.**

Key words: antidiuretic hormone, osmotic demyelination syndrome, sodium.

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## Introduction

Hyponatraemia is defined as a serum sodium under 135 mmol/L. It is the most common electrolyte abnormality and is often a marker of underlying disease. Severe hyponatraemia, defined as a serum sodium of less than 120 mmol/L, occurs in 2.5–6% of inpatients. Hyponatraemia is associated with increased morbidity and mortality (up to 60-fold) in hospitalised patients.<sup>1,2</sup> It is also associated with increased mortality in patients in intensive care, patients with hepatic cirrhosis, congestive heart failure and community-acquired pneumonia, and liver transplant patients who were hyponatraemic at the time of transplantation.<sup>2,3</sup> Severe hyponatraemia is also associated with prolonged hospitalisation and its treatment can cause adverse outcomes including death. Severe hyponatraemia is therefore a medical emergency, requiring intensive care.

## Classification of hyponatraemia

There are several methods of classifying hyponatraemia, and classification based on the fluid status of the patient is the most

easily understood. By far the commonest cause of hyponatraemia in clinical practice is dilutional hyponatraemia due to retention of water in excess of sodium. This requires a deficit in renal water excretion which is usually due to, or accompanied by, an inability to adequately suppress antidiuretic hormone.

### ***Euvolaemic hyponatraemia***

In euvolaemic hyponatraemia the extracellular fluid volume is normal. It is the most common form of hyponatraemia. Causes include:

- syndrome of inappropriate antidiuretic hormone (see Box 1)
- drugs (see Box 2)
- hypothyroidism
- hypocortisolaemia
- primary polydipsia
- exercise-associated hyponatraemia (due to excessive hypotonic fluid intake in the setting of increased antidiuretic hormone secretion).

### ***Hypovolaemic hyponatraemia***

In hypovolaemic hyponatraemia the extracellular fluid volume is reduced. Causes include excessive gastrointestinal losses and salt-losing nephropathies. Cerebral salt wasting is an occasional cause of hyponatraemia in neurosurgical patients or patients with subarachnoid haemorrhage.<sup>4</sup> Thiazide diuretics can cause hypovolaemic hyponatraemia, but are more commonly associated with euvolaemic hyponatraemia.

### ***Hypervolaemic hyponatraemia***

In situations of water and sodium retention, hyponatraemia will result if the water retention exceeds the sodium retention. Extracellular fluid is increased. Cardiac failure, cirrhosis of the liver, renal failure and nephrotic syndrome can cause hypervolaemic hyponatraemia.

### ***Other categories of hyponatraemia***

Hyponatraemia can also be classified by the serum osmolality. Isotonic hyponatraemia can be caused by absorption of irrigating fluid containing glycine, sorbitol or another isosmotic non-sodium compound during urological or gynaecological procedures. Hypertonic hyponatraemia can occur when an osmotically active compound such as glucose or mannitol

### Box 1

#### Causes of syndrome of inappropriate antidiuretic hormone secretion \*

##### Drugs

##### Tumours with ectopic hormone production

- small cell and other pulmonary carcinomas
- pancreatic and duodenal carcinoma
- head and neck malignancies
- mesothelioma
- lymphoma

##### Central nervous system disorders

- infections
- cerebral tumours
- stroke or intracerebral haemorrhage with raised intracranial pressure
- hydrocephalus
- Guillain-Barré syndrome
- multiple sclerosis

##### Pulmonary disease

- pneumonia and other infections
- acute respiratory failure with or without positive pressure ventilation
- asthma
- pneumothorax

##### Miscellaneous

- major thoracic or abdominal surgery
- transphenoidal pituitary surgery
- postoperative pain
- positive pressure ventilation
- HIV/AIDS
- extreme exercise
- hereditary

\* Euvolaemic hyponatraemia with natriuresis and urine osmolality greater than plasma osmolality in patients with normal renal, thyroid and adrenal function

enters the intravascular space in sufficient concentration to pull water from the intracellular to the extracellular space. This causes a dilutional fall in serum sodium while at the same time raising the serum osmolality.

### Clinical assessment

Acute severe hyponatraemia is an emergency which requires a planned and stepwise approach to assessment, investigation and treatment to minimise the harms of this condition and its treatment. The shorter the duration of hyponatraemia the more likely the patient is to be symptomatic and in need of active treatment. Symptoms such as nausea or headache, or the development of lethargy, confusion, coma or seizures, are indicative of acute, or acute on chronic, hyponatraemia and require immediate action.

### Patient history

Is there a history of gastrointestinal or renal disease to suggest excessive solute loss, or a history of excessive fluid intake to suggest exercise-associated hyponatraemia or psychogenic polydipsia? Is there anything in the history (headache, symptoms suggestive of an occult malignancy) to suggest the syndrome of inappropriate antidiuretic hormone secretion? Does the patient have symptoms of hypothyroidism or of Addison's disease?

### Medication history

What is the patient's medication history? Is the patient taking any drugs known to be associated with hyponatraemia (see Box 2)?

### Examination

What is the patient's fluid status – is the patient dehydrated (hypovolaemic hyponatraemia), euvolaemic (euvolaemic hyponatraemia) or fluid overloaded (hypervolaemic hyponatraemia)? Is there evidence of congestive cardiac failure or stigmata of chronic liver disease to suggest hypervolaemic hyponatraemia? Are there any signs of thyroid disease or hypocortisolaemia? Are there any signs suggestive of malignancy as a cause of syndrome of inappropriate antidiuretic hormone secretion?

### Box 2

#### Principal causes of drug-induced hyponatraemia

Diuretics: particularly thiazide diuretics, including combinations with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists

Antidepressants: tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, venlafaxine

Antipsychotics: phenothiazines, haloperidol

Antiepileptics: carbamazepine, oxcarbazepine, valproate, lamotrigine

Antidiabetics: chlorpropamide, tolbutamide

Antibiotics: ciprofloxacin, trimethoprim-sulfamethoxazole, rifabutin

Antiarrhythmics: amiodarone

Antihypertensives: angiotensin converting enzyme inhibitors (angiotensin receptor antagonists), amlodipine

Anticancer/chemotherapeutic drugs: vincristine/vinblastine, cisplatin/carboplatin, alkylating agents, methotrexate, levamisole

Proton pump inhibitors

Non-steroidal anti-inflammatory drugs

Oxytocin, antidiuretic hormone analogues

Amphetamines: MDMA (ecstasy)

## Investigations

When investigating hyponatraemia, it is important to consider whether the sodium result is correct or if there has been a laboratory or sampling error. If investigations suggest a diagnosis of syndrome of inappropriate antidiuretic hormone secretion, further investigations to identify intracranial or intrathoracic pathology or occult malignancy at another site are required.

## Renal function and electrolytes

A low sodium with normal renal function indicates dilutional hyponatraemia either euvolaemic or hypervolaemic, especially if serum urea is low. Impaired renal function, especially with an elevated serum urea, suggests hypovolaemia and hypovolaemic hyponatraemia. A high serum potassium suggests chronic renal disease or, if the urea and creatinine concentrations are only mildly elevated, hypocortisolaemia.

## Osmolality

The serum and urine osmolality should be measured in all patients with hyponatraemia. Serum osmolality will be low in all cases of hyponatraemia except for the rare cases of isotonic or hypertonic hyponatraemia.

The appropriate physiological response to dilutional hyponatraemia is to maximise water excretion by passing maximally dilute urine. The maximal excretory capacity of the kidney is 10–15 L per day and maximally dilute urine has an osmolality of less than 100 mmol/kg. In a patient with dilutional hyponatraemia and normal renal function, urine osmolality greater than 100–150 mmol/kg indicates lack of appropriate suppression of antidiuretic hormone or an inability to maximally dilute the urine due to other mechanisms such as diuretic therapy. In euvolaemic hyponatraemia, with a urinary osmolality of greater than 200 mmol/kg, one of these two abnormalities must be present.

## Urine sodium

The clinical assessment of hydration status is frequently inaccurate so urinary sodium is an important measurement as it assists in the differentiation of the hypovolaemic from the euvolaemic patient.

A urine sodium under 20 mmol/L indicates hypovolaemic hyponatraemia where the sodium loss is of extra-renal origin as the kidneys are reabsorbing sodium. Patients with hypervolaemic hyponatraemia due to cardiac failure, cirrhosis or nephrotic syndrome without renal failure may also have a low urinary sodium.

A urine sodium above 20 mmol/L indicates euvolaemic hyponatraemia of any cause. The urinary concentration of sodium is usually high because of the relatively low urine volume passed in these conditions. High urinary sodium

concentrations can also be seen in hyponatraemia associated with renal salt wasting and renal failure, and in patients on diuretic therapy.

## Endocrine tests

Thyroid function tests should be performed in all patients to exclude hypothyroidism as a cause of hyponatraemia. The possibility of hypopituitarism and Addison's disease should always be considered in the differential diagnosis of hyponatraemia. If there is a clinical suspicion, measure morning cortisol and adrenocorticotrophic hormone (ACTH), with or without a short ACTH stimulation test.

## Treatment of hyponatraemia

In addition to correcting the serum sodium, the management of hyponatraemia must always include treatment of the underlying cause. This could be withdrawing the probable causative drug, treating postoperative pain, treating hormonal abnormalities and treating identifiable causes of the syndrome of inappropriate antidiuretic hormone secretion.

Severe or symptomatic hyponatraemia should be treated as a medical emergency. Failure to act makes progression to altered consciousness, seizures, and permanent brain damage or death probable. These patients must be managed in a hospital with onsite 24-hour pathology and appropriate medical and specialist staffing.

## Euvolaemic hyponatraemia

While fluid restriction is the initial treatment of choice in asymptomatic patients, more active and urgent treatment is required in the symptomatic patient with severe euvolaemic hyponatraemia. It is the commonest type of severe hyponatraemia and prompt intervention to raise the serum sodium is indicated. Isotonic saline is contraindicated as it can be associated with a further fall in serum sodium. Hypertonic saline should only be used in symptomatic patients with very low serum sodium concentrations. The infusion aims to increase the serum sodium to a 'safe' level, usually considered to be greater than 120–125 mmol/L depending on the initial concentration. The rate of increase in serum sodium should be limited to prevent complications. There are a variety of formulae for predicting the increase in serum sodium expected from alterations to the rate and volume of hypertonic saline infusion. However, these formulae often result in over-correction, probably due to alterations in the clinical state not predicted at the time the calculation was performed, such as the commencement of a diuresis following the start of the saline infusion, placing the patient at risk of adverse effects.<sup>5</sup>

A recent review has suggested that immediate treatment should be the infusion of 100 mL of 3% sodium chloride over one hour.<sup>5</sup> If symptomatic hyponatraemia with fitting persists, a further 200 mL over the next two hours can be given. The aim

of treatment is to raise the serum sodium into a 'safe' range usually recognised as greater than 120 mmol/L, and to abolish the patient's symptoms. Once these goals have been achieved further hypertonic saline should not be given, although ongoing fluid restriction will usually be required. It may take 48–72 hours for the patient's symptoms to improve.

The maximum rate of increase in serum sodium should not exceed 10 mmol/L over 24 hours and 18 mmol/L over 48 hours to minimise the risk of osmotic demyelination.<sup>5,6</sup> In patients with liver disease a slower rate of correction is indicated in view of their greater risk of osmotic demyelination. Hypertonic saline can only be administered safely in a hospital with intensive care facilities associated with 24-hour onsite pathology, as the patients must be closely monitored and have their electrolytes checked every two hours. However, the initial infusion of hypertonic saline may need to be given before transfer to that higher level care in consultation with the accepting team.

### **Hypovolaemic hyponatraemia**

The history and clinical examination will be supported by biochemistry consistent with hypovolaemia. The urine sodium will be below 20 mmol/L except in cases of renal salt wasting and renal failure. Treatment consists of volume expansion with isotonic saline. This is the only situation in which the use of isotonic saline is appropriate treatment for hyponatraemia.

### **Hypervolaemic hyponatraemia**

Cardiac failure, hepatic cirrhosis or renal disease should be easily recognisable by history, clinical examination and the results of renal and liver function tests. The management is to treat the underlying disease process and will usually include fluid restriction and diuretic therapy.

### **Complications of treatment**

The treatment of hyponatraemia has been a controversial topic largely due to the recognition of cerebral demyelination ('central pontine myelinolysis', 'osmotic demyelination') as a specific pathological entity associated with hyponatraemia and with the rate and extent of the correction of serum sodium in these patients.

Excessively rapid restoration of serum sodium, and 'overcorrection' of serum sodium above the normal range, have been associated with cerebral demyelination which is irreversible and frequently fatal, and may not be evident for several days after treatment has been completed. The patient recovering from hyponatraemia may deteriorate unexpectedly. Depending on the area of the brain affected, a variety of neurological or psychiatric symptoms may develop. When excessively rapid correction has been recognised, there are reports of lowering serum sodium by various means including the administration of desmopressin to try to avoid osmotic demyelination.<sup>5,7-10</sup>

### **Conclusion**

Severe hyponatraemia is associated with increased morbidity and mortality. When it develops acutely or in hospital and is associated with symptoms, urgent treatment is required. This will usually include the administration of hypertonic (3%) saline in a hospital with 24-hour pathology and intensive care unit services.

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### **Further reading**

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*Conflict of interest: none declared*

### **Self-test questions**

*The following statements are either true or false (answers on page 59)*

1. Cerebral demyelination may develop several days after the correction of severe hyponatraemia.
2. In the management of severe hyponatraemia, the infusion of hypertonic saline should continue for 48 hours after the serum sodium returns to the normal range.