J R Coll Physicians Edinb 2009; 39:154–7

Hyponatraemia

[1]CJ Thompson, [2]RK Crowley
[1]Professor of Endocrinology; [2]Tutor in Endocrinology, Academic Department of Endocrinology, Beaumont Hospital/RCSI Medical School, Dublin, Ireland

ABSTRACT Hyponatraemia is the most common electrolyte abnormality in hospital inpatients, and is associated with complications such as seizures, increased mortality and prolonged hospitalisation. The risk of symptoms, complications and death increases with severity of hyponatraemia. A wide variety of illnesses and therapies can cause hyponatraemia, and the treatment of the underlying condition is always important. There are three main pathophysiological causes of hyponatraemia. Hypovolaemic hyponatraemia is characterised by clinical and biochemical evidence of dehydration and is best treated by intravenous sodium chloride solution. Hypervolaemic hyponatraemia presents with fluid overload, which usually requires diuretic therapy. Euvolaemic hyponatraemia, of which the syndrome of inappropriate antidiuretic hormone secretion is an example, is traditionally treated with fluid restriction, although the new vasopressin antagonists, the vaptans, show great potential for future therapy. An accurate diagnosis of the cause of hyponatraemia is necessary for appropriate treatment. Severe hyponatraemia is potentially life-threatening and, if cerebral irritation is present, intensive therapy with saline infusion may be necessary; because of the risk of central pontine myelinolysis, this should always be given under specialised, highly experienced direction. Plasma sodium should be checked every two hours, and the rate of elevation of plasma sodium concentration should not exceed 0.5 mmol/l/h.

KEYWORDS Euvolaemic hyponatraemia, hypervolaemic hyponatraemia, hypovolaemic hyponatraemia, syndrome of inappropriate antidiuretic hormone

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***November 2008***

Correspondence to ***CJ Thompson, Academic Dept of Diabetes & Endocrinology, Beaumont Hospital, Dublin 9, Ireland***

tel. ***+44 (0)353 1 837 7755***
fax. ***+44 (0)353 1 837 6672***
e-mail ***cthompsonrooms@beaumont.ie***

EDUCATION

INTRODUCTION

Hyponatraemia is the most common electrolyte abnormality observed in hospitalised patients, occurring in 20–30% of acute admissions. Hyponatraemia tends to be more common in the elderly, in patients admitted with respiratory tract infections, in those with a history of alcohol excess and in patients treated with thiazide diuretics (see Table 1).

Hyponatraemia is particularly common in acute neurosurgical admissions and occurs in 50% of patients with subarachnoid haemorrhage. Most patients with a mildly lowered plasma sodium concentration are asymptomatic, but the likelihood of symptoms increases with the severity of the hyponatraemia. Table 2 shows the range of symptoms associated with differences in the severity of the hyponatraemia. There is considerable variation in which symptoms are experienced at any given plasma sodium concentration. The speed of onset of hyponatraemia is the principal determinant of the likelihood of neurological symptoms, with clinical sequelae more likely if the fall in plasma sodium concentration is rapid. Many patients with chronic hyponatraemia resulting from long-term therapy with antipsychotic drugs or thiazide diuretic, for instance, may be relatively free of symptoms, whereas acute water intoxication can produce rapid, profound neurological deterioration. Other factors can also influence the

TABLE 1 Characteristics of patients admitted with severe hyponatraemia and normonatraemia

	Hyponatraemia pNa <125 mmol/l	**Normonatraemia** pNa 135–45 mmol/l	**p**
Age	69 ± 14 years	61 ± 16 years	<0.001
RTI	21%	11%	<0.001
Alcohol excess	11%	3%	<0.001
Thiazide therapy	14%	1%	<0.001
Mortality	27%	10%	0.009
Hospital stay	16 ± 12 days	12 ± 11 days	0.005

pNA = plasma sodium; RTI = respiratory tract infection
Table uses data from Gill et al. (2006)

TABLE 2 Symptoms associated with hyponatraemia

Plasma sodium (mmol/l)	**Symptoms**	**Mortality***
>125	Alert	
120–25	Nausea, headache, altered cognition	23%
115–20	Confusion, stupor	30%
<115	Seizures, coma	50%

*Mortality data derived from Gill et al. (2006)

TABLE 3 Clinical approach to the diagnosis of hyponatraemia

	Clinical characteristics	Causes	
		Urine sodium <30 mmol/l	Urine sodium >30 mmol/l
Hypovolaemic	Tachycardia, postural hypotension, dry skin, reduced skin turgor, raised blood urea, raised plasma renin	Vomiting Diarrhoea Burns Heat exposure (sweating)	Diuretics Addison's disease CSWS Salt-losing nephropathy
Euvolaemic	Blood urea normal or slightly reduced	Hypothyroid Any cause + hypotonic fluid	SIADH ACTH deficiency
Hypervolaemia	Peripheral, sacral, pulmonary oedema Ascites Raised JVP or CVP	Nephrotic syndrome Cardiac failure Liver failure	Renal failure Cardiac failure + diuretics

CSWS = cerebral salt-wasting syndrome; SIADH = syndrome of inappropriate antidiuretic hormone; ACTH = adrenocorticotrophic hormone; JVP = jugular venous pressure; CVP = central venous pressure

impact of hyponatraemia, with co-existing hypoxia, hypercapnia, acidosis, or intracranial lesions making symptoms more likely. Neurosurgical conditions are particularly likely to be symptomatic, with the combination of the neurological insult, hyponatraemia, raised intracranial pressure and surgical intervention.

Hyponatraemia is also associated with significant morbidity and mortality. Gill and colleagues reported a three-fold increase in mortality in patients admitted to a general hospital with a plasma sodium of <125 mmol/l, compared with normonatraemic controls, and the mortality increased with severity of hyponatraemia. Other studies have shown mortality increased up to 60-fold in patients admitted with plasma sodium concentrations <120 mmol/l. These figures reflect the poor prognosis for conditions associated with hyponatraemia and the hazards of inappropriate interventions, as well as emphasise the fact that hyponatraemia is a powerful predictor of mortality and a consistent marker for a prolonged hospital stay.

INVESTIGATION OF HYPONATRAEMIA

There are a wide variety of conditions that produce symptomatic hyponatraemia in clinical practice and treatment depends on accurate identification of the precipitating pathology. Incorrect diagnosis can lead to erroneous and possibly dangerous therapy. A list of causes of hyponatraemia is shown in Table 3. There are a number of algorithms for the diagnostic approach to hyponatraemia and they all have merit and adherents, but the approach summarised in Table 3 is one that we have found to be practical and easy to use for general physicians and non-consultant hospital doctors, as well as endocrinologists.

The key diagnostic step is to assess the blood volume status of the patient both clinically and biochemically. Although this may sometimes be difficult, a reasonable estimation can be made with simple bedside parameters, and measurement of blood urea; measurement of central venous pressure is very useful if available. The next step is to see whether sodium is being conserved or lost by the kidneys, and the urine sodium is valuable. A spot urine sodium is less accurate than a timed collection, but the latter is less practical, as a diagnosis is required immediately, and treatment such as diuretic therapy or intravenous fluids can alter the urine sodium concentration. The urine sodium cut-offs in Table 3 do have some diagnostic latitude, but they are good guidelines upon which to make a diagnosis.

The most common error in clinical practice is to ascribe every case of hyponatraemia to be secondary to syndrome of inappropriate antidiuretic hormone (SIADH). It is important to stress that there are a number of minimum criteria that must be met before the diagnosis of SIADH is made. These are summarised in Table 4. It is important to note that any urine osmolality greater than 100 mOsm/kg in the presence of hyponatraemia indicates inappropriate urine concentration; it is not necessary, as some textbooks claim, for the urine osmolality to exceed the plasma osmolality in order to diagnose SIADH. Although physiological studies show that plasma volume is slightly expanded in SIADH, this is not clinically obvious, and convention dictates that SIADH is included in the category of euvolaemic hyponatraemia.

TABLE 4 Essential criteria for the diagnosis of SIADH

Plasma sodium <135 mmol/l
Urine osmolality >100 mOsm/kg
Urine sodium >30 mmol/l
Patient clinically euvolaemic
Exclusion of glucocorticoid deficiency
Hyponatraemia
Normal salt intake

The exclusion of glucocorticoid deficiency is important. Addison's disease, which is characterised by deficiency of both cortisol and aldosterone and which manifests as

EDUCATION

TABLE 5 Causes of SIADH

Tumours	Lung, pancreas, ureter, stomach, testis
Pulmonary	Pneumonia, abscess, empyema, suppurative lung disease, positive pressure ventilation, fibrosis, tuberculosis
Central nervous system	Tumours, abscess, meningitis, encephalitis, (subarachnoid, subdural or intracranial) haemorrhage, traumatic brain injury, cranial surgery or hypophysectomy, demyelination
Drugs	Selective serotonin reuptake inhibitors (SSRIs), phenothiazines, haloperidol, tricyclic antidepressants, chlorpropamide, methylenedioxymethamphetamine (MDMA; 'ecstasy'), vincristine
Miscellaneous	HIV disease, idiopathic

hypovolaemic hyponatraemia with hyperkalaemia, is unlikely to be confused with SIADH. Isolated cortisol deficiency due to failure to secrete adrenocorticotropic hormone (ACTH), owing to hypothalamo-pituitary disease, however, presents with an identical biochemical profile to classical SIADH. It is easy to miss glucocorticoid deficiency, unless it is specifically tested for in hyponatraemia. Pituitary disease may present with biochemical SIADH in a patient with clinical signs of hypogonadism, and ACTH deficiency should be strongly suspected in any patient with intracranial disease, such as traumatic brain injury or subarachnoid haemorrhage, who presents with 'SIADH'. Up to 10% of cases of 'idiopathic SIADH' are estimated to be secondary to glucocorticoid deficiency, which emphasises the need to include a synacthen test as part of the routine battery of investigations of euvolaemic hyponatraemia. A full list of causes of SIADH is shown in Table 5.

The investigation of possible SIADH should include urea and electrolytes, plasma and urine osmolality, urine sodium concentration, assessment of blood volume, thyroid function tests and short synacthen testing for glucocorticoid reserve. If the onset of hyponatraemia is rapid and coincides with a brain insult, it is important to remember that there may be a normal cortisol response to synacthen, if there has not been time for adrenal atrophy to follow pituitary failure. A careful assessment of baseline cortisol in the context of acute illness may suggest ACTH deficiency, although tests of the integrity of the entire hypothalamo–pituitary–adrenal axis, such as the insulin tolerance test or glucagon test may be indicated. Plasma vasopressin concentrations are elevated in more than 90% of cases of hyponatraemia, irrespective of aetiology. The assay for vasopressin is available in only a few centres and results can take several weeks to be returned. Therefore, the measurement of vasopressin is rarely valuable in the investigation of hyponatraemia.

If a diagnosis of SIADH is established, a careful drug history, including the period prior to hospital admission, may reveal an underlying pharmacological cause. Weight loss may suggest underlying malignancy and the need for thoracic and abdominal scanning, and brain imaging is indicated to exclude intracranial pathology.

MANAGEMENT OF HYPONATRAEMIA

The management of hyponatraemia depends entirely on the underlying diagnosis.

Hypovolaemic hyponatraemia

Restoration of blood volume with intravenous saline is the key issue. It is important to discontinue diuretic therapy where relevant. The treatment of the underlying illness – corticosteroid therapy in Addison's disease, for instance – is also important.

Euvolaemic hyponatraemia

First-line treatment remains fluid restriction, but it is essential to exclude volume depletion before this therapy is instituted. To be effective, fluid restriction needs to be set at 800–1,200 ml/24 hours and not all patients are able to maintain this, particularly once they are discharged from hospital. Demeclocycline, which renders the renal tubules resistant to the antidiuretic action of vasopressin, is the traditional second-line treatment. It is sometimes slow to act and has a number of side effects, including photosensitive rashes. Occasionally, patients can develop marked polyuria with hypernatraemic dehydration, so patients must be monitored closely. In cases of diagnostic doubt, it is worthwhile trying a clinical trial of intravenous normal saline, which has been reported to be effective in 50% of cases of SIADH, though the suspicion remains that some of these patients had undiagnosed hypovolaemic hyponatraemia. The new vasopressin antagonists, or vaptans, have been extensively investigated and found to be safe and effective agents that promote steady, sustained aquaresis and elevation in plasma sodium concentrations. They promise to become first-line therapy in the future but are currently only available, as intravenous therapy, in the USA.

Hypervolaemic hyponatraemia

Fluid overload is treated with diuretics, together with therapy directed to the underlying condition that precipitated hyponatraemia. The vaptans have been extensively investigated in the treatment of hypervolaemic hyponatraemia, particularly in congestive cardiac failure, and offer promise in promoting clinically important aquaresis and the restoration of plasma sodium concentrations towards normal.

Central pontine myelinolysis

A rapid elevation of plasma sodium concentration in patients with chronic hyponatraemia can lead to the catastrophic condition of central pontine myelinolysis, which is characterised by coma/confusion, quadriplegia and cranial nerve defects. However, in cases where cranial irritation, due to hyponatraemic coma or seizures,

EDUCATION

J R Coll Physicians Edinb 2009; 39:154–7

can produce irreversible brain damage, fluid restriction alone is insufficient to elevate plasma sodium concentration to a level that prevents brain injury. In this situation, hypertonic saline infusion may be indicated as a life-saving or brain-preserving measure. However, as too rapid elevation of plasma sodium can cause central pontine myelinolysis, hypertonic saline should only be used with caution and with two-hourly measurement of plasma sodium concentration, to ensure that the rate of rise of plasma sodium concentration is not too rapid.

Patients with acute hyponatraemia are not as vulnerable to central pontine myelinolysis, but in chronic hyponatraemia the brain adapts to the hyponatraemic milieu and rapid elevation of plasma sodium concentration in this circumstance is associated with increased risk of central pontine myelinolysis. Patients with chronic alcoholism, as well as young pregnant females, are also prone to the development of central pontine myelinolysis.

There are a number of guidelines for management of severe hyponatraemia with intravenous hypertonic saline (see Further Reading). Most have to be adapted to the individual patient and to the rate of rise in plasma sodium concentration; a simple practical guideline is to start 3% sodium chloride at 500 ml over 24 hours and adjust the rate of infusion to cause a steady rise in plasma sodium concentration of not more than 6 mmol/l over 12 hours, or not more than 4 mmol/l over 12 hours in alcoholics. It is usual practice to discontinue intravenous saline once a plasma concentration exceeds 120 mmol/l, or once there has been a total rise of 12 mmol/l in 24 hours.

Hypertonic saline infusion is a hazardous therapy, which should only be undertaken with measurement of plasma sodium a minimum of every two hours, and under the supervision of an experienced physician.

FUTURE DEVELOPMENTS

The continued clinical research into the clinical application of the vaptan family of vasopressin antagonist drugs is likely to contribute significantly to our ability to safely and effectively manage euvolaemic and hypervolaemic hyponatraemia.

KEY POINTS

- Hyponatraemia is the most common electrolyte abnormality in hospitalised patients and contributes to excess morbidity and mortality and to increased duration of hospital stay.
- Hyponatraemia is not always syndrome of inappropriate antidiuretic hormone (SIADH).
- An assessment of blood volume status and urine sodium measurement is essential for accurate diagnosis of the cause of hyponatraemia.
- The treatment of hyponatraemia is dictated by accurate diagnosis of the cause of hyponatraemia.
- Always consider adrenocorticotropic hormone deficiency as a cause of syndrome of inappropriate antidiuretic hormone, particularly in patients with a history of intracranial disease.
- Check serum sodium every two hours and NEVER increase serum sodium >12 mmol per 24 hours.

FURTHER READING

- Gill GV, Huda MSB, Boyd A et al. Characteristics and mortality of severe hyponatraemia – a hospital-based study. *Clin Endocrinol (Oxf)* 2006; 65:246–9.
- Loh JA, Verbalis JG. Disorders of water and salt metabolism associated with pituitary disease. *Endocrinol Metab Clin North Am* 2008; 37:213–34.
- Schrier RW, Gross P, Gheorgiade M et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; 355:2099–112.
- Sherlock M, O'Sullivan E, Agha A et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol (Oxf)* 2006; 64:250–4.
- Smith D, McKenna K, Thompson CJ. Hyponatraemia. *Clin Endocrinol (Oxf)* 2000; 52:667–78.
- Verbalis JG, Goldsmith SR, Greenberg A et al. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* 2007; 120(11 Suppl 1):S1–S21.

Originally published as part of the Diabetes & Endocrinology module in the RCPE Online Continuing Medical Education Programme. Online CME, including self-asessment MCQs, is available to Fellows and Members at: http://www.rcpe.ac.uk

EDUCATION