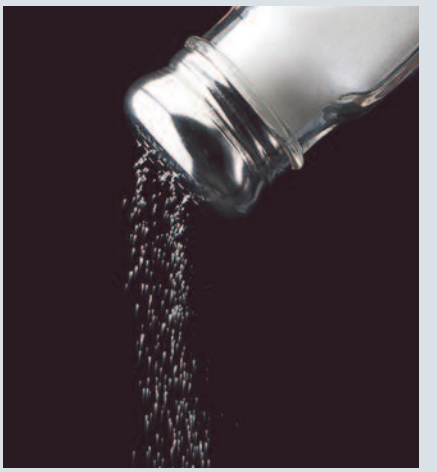
Investigating disorders of hyponatraemia

BOBBY CHAN MB BS, FRACP
ANTHONY J. O'SULLIVAN MB BS, FRACP, MD, MHPEd



The investigations in endocrinology section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

Hyponatraemia, defined as an excess of water in relation to the sodium in the extracellular fluid, occurs in 15 to 20% of hospitalised patients and constitutes a common serum electrolyte abnormality.[1] Hyponatraemia is reported to be associated with increased morbidity and mortality in patients with heart, liver or neurological diseases.[2-7] Even mild chronic hyponatraemia has been associated with subtle neurological defects, manifested as impairments in balance and attention that can increase the incidence of falls.[8] In normal individuals, the sodium concentration is controlled by the release of antidiuretic hormone, also called vasopressin, which is the principal determinant of renal water excretion. Antidiuretic hormone secretion is mainly controlled by serum osmolality.

There are several potential causes of hyponatraemia (see the box on this page), but the most common cause is often due to an impairment of renal water excretion. It is important to determine whether hyponatraemia is hypovolaemic, euvolaemic or hypervolaemic because treatment differs for each. In clinical practice, the diagnosis of hyponatraemia can be difficult because more than one aetiology may be the present.

The following series of three case vignettes demonstrate the correct approach to the investigation and management of hyponatraemia.

Case 1

An 87-year-old woman presents with nausea. She has a background history of hypertension (treated with irbesartan and hydrochlorothiazide), atrial fibrillation (treated with warfarin), achalasia and glaucoma. On examination she is euvolaemic and the rest of the examination is unremarkable. The results of the investigations are as follows:

- ***serum sodium level: 118 mmol/L (normal range: 135–145 mmol/L)***
- ***serum potassium level: 4.2 mmol/L (normal range: 3.6–5.1 mmol/L)***
- ***serum creatinine level: 86 µmol/L (normal range: 60–110 µmol/L)***
- ***chest x-ray possibly showing a rounded density lesion overlying the right 4th and 5th ribs anteriorly***
- ***blood thyroid-stimulating hormone (TSH) and 8 am morning plasma cortisol levels both in the normal range.***

What further investigations should be ordered?

This patient has euvolaemic hyponatraemia and the most common cause is the syndrome of inappropriate antidiuretic hormone (SIADH). Laboratory tests that will provide important initial information are serum osmolality, urine osmolality and urine sodium concentrations. Use of medications (e.g. thiazides) is also a common cause of hyponatraemia (see the box on this page); therefore, it is important to review the patient's medication list. In this

Causes of hyponatraemia

Hypovolaemic hyponatraemia

- Renal sodium losses
  - diuretics (frusemide, thiazides, indapamide)
  - adrenal insufficiency
  - salt-wasting nephropathy
- Extra-renal losses
  - diarrhoea, stoma loss
  - vomiting
  - excessive sweating
  - third space loss (pancreatitis, burns)

Euvolaemic hyponatraemia

- Syndrome of inappropriate secretion of antidiuretic hormone
  - malignancy (e.g. small cell lung carcinoma, head and neck tumours)
  - cerebral pathology (e.g. stroke, haemorrhage and trauma)
  - respiratory pathology (e.g. infection, asthma and pneumothorax)
  - drugs (e.g. selective serotonin reuptake inhibitors, cyclophosphamide, carbamazepine, tricyclic antidepressants)
  - idiopathic
- Psychogenic polydipsia
- Reset osmostat
- Hypothyroidism
- Adrenal insufficiency (maybe hypovolaemia as well)
- Beer potomania
- Inadequate intake of solutes

Hypervolaemic hyponatraemia

- Congestive heart failure
- Chronic renal failure
- Liver cirrhosis

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Dr Chan is an Advanced Trainee in Endocrinology at St George Hospital, Kogarah, Sydney. Associate Professor O'Sullivan is an Associate Professor in Medicine at The University of New South Wales; and Head of the Department of Endocrinology at St George Hospital, Kogarah, Sydney, NSW.

SERIES EDITOR: Dr Bernard Champion BEc, MB BS, BSc(Med)(Hon 1), FRACP, MMedEd is a Lecturer at Sydney Medical School Nepean and The University of Sydney; and Head of Department at Endocrinology and Diabetes, Nepean Blue Mountains Local Health District, Sydney, NSW.

case the diuretic may also be contributing to some salt loss.

The results show:

- serum osmolality: 258 mmol/kg (normal range: 275–295 mmol/kg)
- urine osmolality: 420 mmol/kg (normal range: 300–900 mmol/kg)
- urine sodium level: 76 mmol/L
- repeat urine sodium level after diuretic cessation: 56 mmol/L.

How should the above results be interpreted?

In general, if a patient is euvolaemic, the serum osmolality is less than 275 mmol/kg, and there are inappropriately elevated urine osmolality (more than 100 mmol/kg and usually more than 300 mmol/kg) and urinary sodium (more than 30 mmol/L) concentrations, then the diagnosis is likely to be SIADH. As this patient was taking a diuretic when investigations were carried out, technically SIADH cannot be diagnosed. Measurement of urine sodium level was therefore repeated after diuretic cessation. The repeat urine sodium level will remain greater than 30 mmol/L in true SIADH; however, a low urinary sodium level may indicate salt depletion.

What is the diagnosis?

The results above are consistent with a diagnosis of SIADH. This is a condition in which the degree of antidiuretic hormone secretion is inappropriately high for the serum osmolality and, therefore, free water is retained, leading to hyponatraemia.

What is the cause of this patient's SIADH?

There are many causes of SIADH (see the box on page 38). The risk of developing SIADH rises with increasing age and is especially high among nursing home residents.[9] Common causes are malignant diseases, pulmonary disease and disorders of the central nervous system.[10] In some cases the cause of SIADH is not found.

What further investigations are required?

Further imaging is required in this case due to the findings on chest x-ray. A chest CT scan was carried out and showed no focal lung nodule or consolidation.

How should this patient be managed?

Fluid restriction is the cornerstone of therapy for people with SIADH, and 0.5 to 1.0 L of fluid daily is usually enough to gradually correct hyponatraemia. In extreme cases, less than 500 mL of fluid is required. Investigation of the underlying cause of SIADH is warranted according to the clinical picture.

This patient's irbesartan and hydrochlorothiazide were ceased on admission to hospital and her blood pressure was closely monitored. Her serum sodium level normalised after six days of fluid restriction. On discharge her fluid restriction was relaxed and her irbesartan was reintroduced. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers have been reported to be associated with hyponatraemia. Cessation of these medications potentially allows a more normal physiological recovery of fluid and electrolyte balance.

Case 2

A 47-year-old obese man with hyponatraemia is referred to a specialist by his GP. Apart from some intermittent vomiting, the patient is otherwise asymptomatic. He is currently taking indapamide for his hypertension. He admits to drinking 12 standard beers a day and has not been eating well. On examination, he had pitting oedema but no other signs of chronic liver disease. His blood tests are as follows:

- ***serum sodium level: 115 mmol/L (normal range: 135–145 mmol/L)***
- ***serum creatinine level: 121 mmol/L (normal range: 60–110 µmol/L)***
  serum albumin level: 29 g/L (normal range: 32–55 g/L)
- ***serum alkaline phosphatase level: 156 IU/L (normal range: 0–180 IU/L)***
- ***serum gamma glutamyl transferase: 378 IU/L (normal range: 1–52 IU/L)***
- ***international normalised ratio (INR): 1.3 (normal range: 0.9–1.1).***

What should be done next?

Sometimes, patients can present with a mixed picture and fluid status might be hard to determine. Indapamide is one of the many medications that can cause hyponatraemia. Investigations for other causes of hyponatraemia in this patient include measurement of serum osmolality, urine osmolality and urine sodium concentrations, and TSH and 8 am morning cortisol levels.

The results show:

- serum osmolality: 270 mmol/kg (normal range: 275–295 mmol/kg)
- urine osmolality: 165 mmol/kg (normal range: 300–900 mmol/kg)
- urine sodium level: less than 10 mmol/L
- TSH level: 3.7 mIU/L (normal range 0.27–4.2 mIU/L)
- serum cortisol level: 370 nmol/L (normal range: 155–600 nmol/L).

Although this patient has a serum osmolality of less than 275 mmol/kg and a urine osmolality of more than 100 mmol/kg, his urine sodium level is less than 10 mmol/L and, therefore, does not correlate with a diagnosis of SIADH. The low urine sodium level is consistent with salt depletion. The normal TSH and morning cortisol levels make hypothyroidism and adrenal insufficiency unlikely; however, adrenal insufficiency may present with a cortisol level in the low-normal range and, if clinically indicated, further investigations would be required.

What is the diagnosis?

People who are heavy beer drinkers or are malnourished may have a marked reduction in water excretion because solutes are required for water excretion.[11] Beer contains little sodium, potassium or protein, resulting in poor dietary intake of solutes. This leads to a reduction in urea and solute excretion, resulting in reduced urine output of water and fluid retention. This patient, therefore, has hyponatraemia secondary to low dietary solute intake, vomiting and fluid retention. The diuretic may also be contributing to salt depletion.

How should this patient be managed?

The patient should have his fluids restricted to about 500 mL per day and receive intravenous infusion of normal sodium chloride. Indapamide should be ceased. Serum sodium levels should not be increased by more than 10 mmol/L per 24-hour period.

The patient's sodium level returned to normal within seven days. He was referred to the drug and alcohol team as an inpatient and counselled about reducing his alcohol consumption. A dietitian review was also performed due to his low albumin level and oral thiamine was started. Due to his deranged liver function test, low albumin level and high INR, he is likely to have developed chronic liver disease and he was referred to a liver clinic for further investigation and management.

Case 3

A 38-year-old woman presents with general weakness, lethargy, dizziness, vomiting and weight loss. This is on a background history of autoimmune hypothyroidism for which she is currently taking thyroxine. On examination she is hypotensive (blood pressure: 88/60 mmHg with a postural drop) and mildly dehydrated. She is noted to have generalised skin pigmentation. She has no signs of infection or pituitary disease.

Full blood count and liver function tests were unremarkable. Other results show:

- ***serum sodium level: 113 mmol/L (normal range: 135–145 mmol/L)***
- ***serum potassium level: 5.6 mmol/L (normal range: 3.6–5.1 mmol/L)***
- ***serum creatinine level: 86 µmol/L (normal range: 60–110 µmol/L)***
- ***serum osmolality: 255 mmol/kg (normal range: 275–295 mmol/kg)***
- ***urine osmolality: 280 mmol/kg (normal range: 300–900 mmol/kg)***
- ***urine sodium level: 45 mmol/L.***

This patient has symptomatic hyponatraemia and hyperkalaemia.

What investigations should be ordered?

This woman's symptoms and signs are consistent with primary adrenal failure. The lack of adrenal steroid production leads to an inability to retain salt and water leading to hyponatraemia and dehydration. SIADH is unlikely to be due to the dehydration and postural hypotension. The increase in serum potassium level results from reduced potassium excretion related to hypoaldosteronism. Patients with adrenal failure, either primary or secondary, may have clinical manifestations, such as weakness, fatigability, anorexia, orthostatic hypotension, nausea, vomiting and hyponatraemia. In patients with primary adrenal failure, hyperpigmentation can be seen due to greatly increased secretion of adrenocorticotropic hormone (ACTH) because of loss of adrenal feedback suppression. An urgent random cortisol measurement should be the first initial investigation in this case. Corticosteroids will generally need to be administered immediately depending on the clinical situation.

The results show:

- morning cortisol level: 43 nmol/L (normal range: 155–599 nmol/L)
- ACTH level: 144 pmol/L (normal range: 0–11.1 pmol/L)
- thyroid function test results were normal.

What is the diagnosis?

The high ACTH level and the very low cortisol level are diagnostic of primary adrenal failure.

How should this patient be managed?

This woman needs immediate cortisol replacement therapy. The patient must not be fluid restricted. Normally in acute presentations, intravenous hydrocortisone is used. For patients with severe hypotension, aggressive fluid therapy with intravenous normal sodium chloride is required. After the patient has been stabilised, she can then gradually start oral adrenal replacement therapy in the form of cortisone acetate 25 mg in the morning and 12.5 mg at night (or an equivalent corticosteroid); however, lower doses may be appropriate depending on the clinical situation. Mineralocorticoid treatment is likely to be warranted. There is no indication to image the adrenal glands in autoimmune adrenal disease; however, if another cause of adrenal failure is possible (metastases or tuberculosis), imaging may be warranted.

This patient has autoimmune adrenal failure combined with autoimmune hypothyroidism. She requires life-long thyroxine and adrenal replacement therapy. She requires periodic review for other autoimmune diseases plus advice on the risk of first-degree relatives developing autoimmune endocrine disorders.

What should we tell this patient?

The patient needs to be aware that she requires cortisone treatment indefinitely. She cannot go a 24-hour period without taking cortisone. If she is unable to take her medication orally she should seek immediate medical care and will require parenteral corticosteroids. She should have parenteral corticosteroids at home for emergency administration. She also needs to be aware that she should increase her cortisone dose when she has intercurrent illnesses, such as the flu or other physical or emotional stresses. She needs to obtain a bracelet or necklace to notify others that she requires cortisone treatment.

Support groups, such as the Australian Addison's Disease Association, are important for this patient. She should be made aware that she should increase her salt intake and fluids when she exercises. **ET**

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