Managing drug-induced hyponatraemia in adults

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SYNOPSIS

Drug-induced hyponatraemia is commonly associated with diuretics, selective serotonin reuptake inhibitors and antiepileptics. With increasing polypharmacy and an ageing population, the prevalence of drug-induced hyponatraemia is likely to increase. Most patients with drug-induced hyponatraemia are asymptomatic and the diagnosis is made incidentally following routine blood tests. Mild cases may be managed either by stopping the drug or by careful observation if the drug is considered essential. More severe hyponatraemia may require fluid restriction in the short term as well as withdrawal of the causal drug. Referral may be required for patients with acute illness and for those with severe and/or refractory hyponatraemia.

Index words: adverse effects, diuretics, antidepressant drugs, sodium.

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Introduction

Hyponatraemia is defined as a serum sodium concentration below 135 mmol/L. It occurs commonly and is often discovered on a routine blood test. A Melbourne laboratory found hyponatraemia in 4.8% of 326 923 samples from ambulatory patients and 14% of 84 464 samples from admitted patients referred by general practitioners. In these patients, serum sodium was less than 115 mmol/L in 0.3%, 115–124 mmol/L in 4% and 125–135 mmol/L in 96% (L. Eilermann, Melbourne Pathology, personal communication 2002).

Although drugs are a common cause of hyponatraemia, other causes should be considered (Table 1).[1] Assessing the patient's fluid status and plasma osmolality can help in finding the cause. As hyponatraemia is often associated with fluid retention (dilutional hyponatraemia) the osmolality is usually reduced, however other causes may be associated with normal or increased osmolality.

In normovolaemic patients the syndrome of inappropriate secretion of antidiuretic hormone is the most frequent mechanism for hyponatraemia. Drugs are often responsible for this syndrome, but may cause hyponatraemia in other ways (Table 2). In Australia, drug-related hyponatraemia is most commonly reported in association with diuretics and selective serotonin reuptake inhibitors (SSRIs), but other drugs can be implicated (Table 3).

With mild drug-related hyponatraemia the drug should be stopped where possible, but if the drug is essential continue it

Table 1

Causes of hyponatraemia *

Hypotonic hyponatraemia

Reduced water excretion

Increased extracellular fluid volume

congestive cardiac failure, cirrhosis, nephrotic syndrome, renal failure

Normal extracellular fluid volume

- thiazide diuretics
- hypothyroidism, adrenal insufficiency
- syndrome of inappropriate secretion of antidiuretic hormone
  - many drugs (see Table 2)
  - cancers
  - disorders of the central nervous system
  - pulmonary disorders
  - severe nausea and/or pain
- decreased salt intake

Decreased extracellular fluid volume

- renal sodium loss e.g. diuretics, osmotic diuresis, adrenal insufficiency, salt-wasting nephropathy
- extra-renal sodium loss e.g. diarrhoea, vomiting, sweating, fluid sequestration in 'third space' in surgical patients

Excess water intake

- primary polydypsia
- low sodium irrigations or infusions during procedures
- tap water enemas
- dilute infant formulae

Isotonic hyponatraemia

- pseudohyponatraemia associated with severe hyperglycaemia, hypertriglyceridaemia and hyperproteinaemia
- spurious hyponatraemia in blood taken proximal to dextrose infusions

Hypertonic

- increased extracellular, non-permeable solute e.g. glucose, hypertonic mannitol

* adapted from reference 1

Table 2

Probable mechanisms of drug-induced hyponatraemia

Class	*Mechanism*
Diuretic	decreases total body sodium
SSRI and MAOI	SIADH
Anticonvulsant carbamazepine	SIADH
ACE inhibitor	SIADH ?
NSAID	SIADH
Hormone analogues desmopressin (DDAVP) oxytocin	exogenous antidiuretic hormone

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
SIADH syndrome of inappropriate secretion of antidiuretic hormone
ACE angiotensin converting enzyme
NSAID non-steroidal anti-inflammatory drug

while monitoring the hyponatraemia. When hyponatraemia is more marked short-term fluid restriction and medication withdrawal may be required. In other circumstances (Table 4) referral is advisable.

Assessment

The management of a patient with hyponatraemia depends on their clinical status and the likelihood that one or more drugs are responsible. Assessment and management should consider the following:

- hyponatraemia is often found in healthy and/or asymptomatic people
- most hyponatraemic patients have no symptoms or signs of hyponatraemia
- although neurological symptoms like restlessness, confusion, seizures and drowsiness, can result from hyponatraemia, there may be alternative explanations, even in patients with alarmingly low serum sodium concentrations
- alternative explanations for hyponatraemia including cardiac, liver or renal failure should be considered
- a latent tendency for hyponatraemia may only become apparent when fluid intake is increased, e.g. when fluids are 'pushed' after admission to hospital
- serum sodium measurements, or a battery of tests including sodium, may be specifically requested for sound clinical reasons, or included in tests primarily undertaken for other reasons.

The history and examination will often establish the cause of hyponatraemia, but measuring plasma osmolality can sometimes help in the differential diagnosis.

Diagnostic and therapeutic issues are illustrated in the following case studies.

Table 3

Drugs commonly associated with hyponatraemia

Class	*Drug*	*Number of reports **
Diuretic		
thiazide	indapamide	180
	chlorothiazide	16
combination	amiloride/hydrochlorothiazide	116
loop	frusemide	62
Antidepressant		
SSRI	sertraline	130
	fluoxetine	50
	paroxetine	46
	citalopram	35
	venlafaxine	49
MAOI	moclobemide	19
Antipsychotic	clozapine	14
Anticonvulsant	carbamazepine	101
ACE inhibitor	enalapril	21
	captopril	12
ACE inhibitor/diuretic	perindopril/indapamide	18
COX-2 inhibitor	celecoxib	24
Hypnotic	temazepam	13
Chemotherapeutic	vincristine, vinblastine, carboplatin, cisplatin, cyclophosphamide	25
Sulfonylurea	glipizide, glimepiride, glibenclamide, gliclazide	
Hormone analogue	desmopressin (DDAVP), oxytocin	
Proton pump inhibitor	omeprazole, pantoprazole	
Recreational	3,4 MDMA ('ecstacy')[4]	

* Numbers are given when there were more than 10 spontaneous reports to the Australian Adverse Drug Reactions Advisory Committee 1972–2002. These numbers do not give the rate of adverse drug reactions.

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
ACE angiotensin converting enzyme
COX cyclo-oxygenase
MDMA 3,4-methylenedioxymethamphetamine

Table 4

Hyponatraemia: clinical features to raise concern

Acute illness

Neurological symptoms – increasing confusion, decreasing conscious state, seizures

Dehydration – postural hypotension, tachycardia, oliguria

Fluid overload related to comorbid chronic disease – cardiac, renal or liver disease

Worsening hyponatraemia or failure to respond to treatment

Severe hyponatraemia – (Na+ < 120 mmol/L)

Case 1: Incidental hyponatraemia

You request 'serum creatinine and electrolytes' after deciding to check the renal function of a woman 77 years of age who has proteinuria on 'dipstick' testing. She feels and looks well, has no new symptoms, but has type 2 diabetes, osteoporosis, depression and hypertension. Her medications are alendronate, gliclazide, aspirin, perindopril and amlodipine. She started paroxetine 18 months ago for a relapse of depression.

Serum creatinine is normal, but sodium is 127 mmol/L. According to your records, serum sodium was within normal limits two years ago.

What is the differential diagnosis?

- drug-induced hyponatraemia – paroxetine, perindopril
- 'pseudohyponatraemia' resulting from hyperglycaemia
- dehydration
- occult comorbidities
  - endocrine – hypothyroidism, hypoadrenalism
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion
  - cardiac, renal or liver disease. These are unlikely if she is otherwise well.

What is the most likely cause?

The most likely cause is the SSRI paroxetine. The prevalence of significant hyponatraemia has not been determined from large prospective studies, but a retrospective Australian study showed that the risk is 5.6 times higher in elderly psychiatric inpatients taking SSRIs or venlafaxine than in controls.[2] Hyponatraemia is more likely in older patients and in those taking other drugs associated with hyponatraemia, such as diuretics. In such patients serum sodium should be checked before and several weeks after starting an SSRI.[2]

How would you manage this patient?

A careful history and examination are needed to exclude non-drug causes of hyponatraemia. In an elderly patient like this, the possibility of dehydration and hypothyroidism should be considered. Blood glucose measurement is required to exclude pseudohyponatraemia.

Glucose expands the plasma volume creating an additional sodium-free space. Blood glucose concentrations above 20 mmol/L can therefore spuriously reduce the serum sodium concentration measured by flame photometry. Treatment of the hyperglycaemia should return the sodium concentration to normal. Marked hypertriglyceridaemia and hyperproteinaemia can also cause pseudohyponatraemia in the same way as hyperglycaemia.

Once pseudohyponatraemia has been excluded the most likely cause is paroxetine, which could be continued, as the serum sodium is not dangerously low. Measurement of serum and urine osmolality and urinary sodium might support the diagnosis of inappropriate secretion of antidiuretic hormone related to the SSRI, but these additional tests are not essential here.

The patient should be advised not to drink fluids for purely 'social' reasons. Her serum sodium could be re-checked in a week. If her serum sodium falls further, or if she becomes unwell, the SSRI should be ceased and alternative therapy for depression sought. If a non-drug cause of inappropriate antidiuretic hormone secretion is considered likely following a full clinical reassessment and medication withdrawal, a chest X-ray, to exclude a pulmonary cause, or cerebral computerised tomography, seeking a space-occupying lesion, might be requested.

Case 2: Monitoring for hyponatraemia

A 65-year-old smoker has hypertension, hyperlipidaemia, ischaemic heart disease and congestive cardiac failure. He takes lisinopril, frusemide, indapamide, aspirin, simvastatin and carvedilol. He is feeling well, but you request serum creatinine and electrolytes. His potassium, creatinine and blood glucose are normal, but his sodium is 122 mmol/L.

What is the differential diagnosis?

- drug-induced hyponatraemia – indapamide, frusemide, lisinopril
- cardiac failure – fluid overload
- 'pseudohyponatraemia' – resulting from hypertriglyceridaemia
- occult comorbidities
  - liver or renal disease
  - endocrine – hypothyroidism, hypoadrenalism
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion.

What is the most likely cause of his hyponatraemia?

A careful history and examination should focus on the possibilities of both fluid overload and of reduced extracellular fluid (see box opposite). Measure standing and lying blood pressure, pulse rate and jugular venous pressure, and check for peripheral oedema and crackles in the lung bases. If you are satisfied the patient is normovolaemic and there is no clinical suspicion of alternative causes you could assume the hyponatraemia is drug-induced. Although the most likely drug in this case is indapamide[3], frusemide or lisinopril could be responsible or contributory.

How would you manage the patient?

Indapamide should be ceased and gentle fluid restriction and daily weighing is recommended. Electrolytes should be monitored with the expectation that the serum sodium concentration should improve within a week. Alternative treatment may be required for hypertension and heart failure. Should hyponatraemia persist, you may need to consider a trial of withholding frusemide. Tests of serum and urine osmolality and urinary sodium are difficult to interpret in the context of diuretic use and the results will not contribute to the patient's management.

Case 3: Acutely unwell with hyponatraemia

A woman 32 years of age has epilepsy which is well-controlled by carbamazepine. She has been unwell with increasing lethargy and a 10 kg weight loss in three months. For the last three days

she has been nauseated and has vomited twice. She looks unwell, is slightly pigmented and has postural hypotension. Serum sodium is 120 mmol/L and serum potassium and creatinine are slightly increased.

What is the differential diagnosis?

- adrenal insufficiency
- drug-induced hyponatraemia – carbamazepine
- occult comorbidities
  - endocrine e.g. hypothyroidism
  - cardiac, liver or renal disease
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion.

What is the most likely cause?

The most likely cause is adrenal insufficiency given that the woman has hyperpigmentation and mild hyperkalaemia. Although carbamazepine is a recognised cause of hyponatraemia, it is an unlikely cause of hyponatraemia in this patient as the clinical features are so suggestive of adrenal insufficiency.

How would you manage the patient?

The acute management of this patient includes establishing intravenous access, giving 100 mg hydrocortisone and rehydrating her with intravenous normal saline. Other important acute measures include lying the patient supine and arranging for her admission.

Urgent referral to hospital should be considered for all patients with acute illness and significant hyponatraemia. The decision to refer other patients with hyponatraemia for urgent investigation and treatment is based on the key clinical features outlined in Table 4. Such patients may require fluid restriction, saline infusion and close monitoring. In patients with severe hyponatraemia it is especially important not to correct hyponatraemia too quickly, as the osmotic effects may cause irreversible neurological complications, specifically central pontine myelinolysis.

Assessing fluid status

Features of reduced extracellular fluid:

- dry mucous membranes
- tachycardia
- postural hypotension
- oliguria
- increased urine specific gravity
- increased serum urea and creatinine

Features of fluid overload:

- elevated jugular venous pressure
- tachycardia
- tachypnoea
- added heart sounds
- crackles in the lung bases
- oedema

Summary

Drug-induced hyponatraemia occurs in approximately 5% of outpatients and 15% of inpatients. In Australia from 1972 to 2002, the commonest drugs causing hyponatraemia were indapamide, sertraline, amiloride/hydrochlorothiazide, carbamazepine, frusemide and fluoxetine. Most patients with hyponatraemia are diagnosed incidentally on routine blood tests. Non-drug causes of hyponatraemia should always be considered. In the majority of patients hyponatraemia is mild. These patients are asymptomatic and do not require any specific therapy. In severe cases urgent treatment and referral are necessary.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 119)

7. The syndrome of inappropriate secretion of antidiuretic hormone is usually due to a pituitary tumour.
8. Hyperglycaemia can cause pseudohyponatraemia.