

Adverse drug reaction

Drug-induced syndrome of inappropriate antidiuretic hormone secretion

K Belton, S H L Thomas

Drugs are a common cause of electrolyte abnormalities, and a careful drug history is essential in patients in whom these are demonstrated. One of the more common electrolyte abnormalities that may be drug-induced is hyponatraemia.

Case summary

A 50-year-old woman was admitted to hospital complaining of nausea, diarrhoea and abdominal pain. Her medical history included depression, alcoholism and laryngeal carcinoma treated by laryngectomy and radiotherapy. Her drug therapy on admission was atenolol 50 mg and loprazolam 1 mg, each once daily; sertraline 50 mg daily had been started 2 weeks prior to admission.

On examination she was thin but not clinically dehydrated. She was afebrile with a blood pressure of 145/100 mmHg and a pulse of 100 beats/min. She had dry skin and palmar erythema. Abdominal examination was normal. There was no neurological deficit. Chest X-ray, full blood count and clotting were normal, except that the mean corpuscular volume was 104 fl (normal range 78-98 fl). Her erythrocyte sedimentation rate was 30 mm/h, sodium 129 mmol/l (132-144), potassium 3.8 mmol/l (3.5-5.0), urea 5.6 mmol/l, creatinine 98 µmol/l and gamma-glutamyl transferase 151 U/l (5-35). Thyroid function tests were normal. Stool samples were negative for occult blood and *Clostridium difficile* toxin and a stool culture was negative.

The following day the patient suffered two grand mal seizures and was commenced on phenytoin. A computed tomography (CT) scan was normal. Repeat blood tests showed a sodium of 118 mmol/l. Urine and plasma osmolarities were 365 and 253 mOsm, respectively, with a urinary sodium of 28 mmol/l, confirming the diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Random cortisol was normal. Sertraline therapy was discontinued and the patient's fluid intake was restricted. Over the next 24 hours plasma sodium fell further to 110 mmol/l, but the osmolarity, sodium and potassium returned to normal over the next few days and the diarrhoea and abdominal pain resolved. On discharge, and after fluid restriction had been discontinued, the patient's plasma sodium and potassium were 135 mmol/l and 4.6 mmol/l, respectively. The patient took phenytoin for 4 weeks after

Causes of SIADH

Non-drug causes

- ADH-secreting neoplasms: lung, pancreas, lymphoma, thymoma, mesothelioma
- non-neoplastic lung disorders: pneumonia, asthma, tuberculosis, empyema
- CNS disorders: meningitis, encephalitis, cerebral abscess, stroke, hydrocephalus
- other: hypothyroidism

Drug causes

- antidepressants: eg, tricyclics, SSRIs
- antidiabetic drugs: eg, chlorpropamide, metformin
- antineoplastic agents: eg, vinca alkaloids, cyclophosphamide, cisplatin
- antipsychotic drugs: eg, phenothiazines, butyrophenones
- analgesics: eg, non-steroidal anti-inflammatory drugs
- anti-epileptic drugs: eg, carbamazepine, sodium valproate
- diuretics: eg, thiazides, amiloride
- others: eg, alpha interferon, ecstasy

NB: Similar clinical features may also be produced by exogenous administration of antidiuretic hormones such as desmopressin, vasopressin, or oxytocin

Box 1

discharge and then discontinued and has not experienced further convulsions.

Discussion

SIADH, first reported by Bartter and Schwartz in 1967,¹ is an osmoregulatory disorder with a number of causes, including drugs (box 1).² It is associated with impaired water excretion resulting in dilutional hyponatraemia. Plasma osmolarity is reduced (<280 mOsm/kg), while the urine is inappropriately concentrated (urine osmolarity >100 mOsm/kg). The differential diagnosis includes hyponatraemia caused by excessive sodium loss, such as with diuretic therapy, diarrhoea, vomiting or Addison's disease. Drugs are thought to cause SIADH by direct or indirect stimulation of vasopressin release from the posterior pituitary gland, although the mechanism is not known. Symptoms generally present at plasma sodium concentrations less than 130 mmol/l and include anorexia, nausea and vomiting, headache, diarrhoea, weakness, lethargy, confusion, convulsions and coma. Severity is usually

Northern & Yorkshire
Regional Drug and
Therapeutics Centre,
Wolfson Unit of
Clinical
Pharmacology,
University of
Newcastle upon Tyne,
Newcastle NE2 4HH,
UK
K Belton
S H L Thomas

Correspondence to
Dr SHL Thomas

Accepted 9 March 1999

determined by the speed of onset and extent of the fluid and electrolyte disturbances.

In this case other possible causes of hyponatraemia included diarrhoea and vomiting; however she was not clinically or biochemically dehydrated. Her convulsions may have been caused or contributed to by acute alcohol withdrawal, although it is more likely that the rapidly worsening hyponatraemia was responsible. Many of the non-drug causes of SIADH were excluded by the normal chest X-ray and head CT scan. The diagnosis was confirmed by the response to drug withdrawal.

Drug-induced SIADH is treated by withdrawing the suspect drug and restricting fluid intake. This is almost always effective, as in this case. Treatment of severe or persistent hyponatraemia is controversial. If symptoms are severe and the serum sodium is very low (ie, <125 mmol/l), some authorities advocate cautious sodium replacement with normal or hypertonic (5%) saline.^{2,3} This is infused at a rate of up to 75 mmol sodium per hour until the plasma sodium reaches 125 mmol/l. Addition of frusemide may be useful by enhancing the excretion of hypotonic urine. During this process plasma sodium should be measured frequently and not allowed to increase by more than 2 mmol/h and 12 mmol/l per day. The danger of sodium infusion is that it may cause central pontine myelinolysis, particularly in patients with chronic hyponatraemia.^{3,4} This is characterised by flaccid paralysis, bulbar weakness, abnormal eye movements and coma, features which may not resolve when the plasma sodium is stabilised. Demeclocycline is sometimes used to treat chronic SIADH,² but is not usually necessary in drug-induced SIADH since this usually resolves spontaneously once the responsible drug is withdrawn.

The elderly appear to be particularly at risk of developing drug-induced SIADH. In 1994 the CSM/MCA reported on 116 cases of antidepressant-induced hyponatraemia; 88 of these involved selective serotonin re-uptake inhibitors (SSRIs) and the mean age was 73

Learning points

- hyponatraemia is commonly caused by drugs, either because they cause excessive sodium loss (eg, diuretics) or cause inappropriate antidiuretic hormone secretion resulting in dilutional hyponatraemia
- SIADH is diagnosed on the basis of low plasma osmolality associated with inappropriately high urine osmolality and urine sodium
- many drugs may induce SIADH, including SSRI antidepressants. The elderly appear at particular risk
- drug-induced SIADH should be treated by withdrawal of the offending drug and fluid restriction. Sodium infusion is controversial and should only be considered in severe cases
- profound drug-induced hyponatraemia is a serious adverse drug reaction and should be reported to MCA/CSM using a yellow card, even if the suspect drug is already known to cause this effect

Box 2

years.⁵ More recently, a series of 736 cases of SIADH associated with SSRIs has been described. Of these, 75% were over 65 years of age, 75% were female, and 75% involved fluoxetine.⁶ To what extent these figures reflect the characteristics of the population receiving SSRIs, and to what extent the utilisation of the individual agents, remains uncertain. In these cases the median time from onset of hyponatraemia was 13 days, although 29% presented more than 3 months after starting on SSRI therapy. Hyponatraemia was reversed by withdrawal of the SSRI in 96% of the cases described. By February 1998 the CSM/MCA has received 65 reports of SIADH and 305 reports of hyponatraemia associated with SSRIs.

Keywords: adverse drug reaction; hyponatraemia; syndrome of inappropriate secretion of antidiuretic hormone; sertraline

1 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967;42:790–806.

2 Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate ADH secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995;12:209–25.

3 Ayus JC, Krotapalli RK, Arieff AI. Changing concepts in treatment of severe hyponatraemia: rapid correction and possible relationship to central pontine myelinolysis. *Am J Med* 1985;78:897–902.

4 Sterns RH, Riggs JE, Schochet Jr SS. Osmotic demyelination syndrome following correction of hyponatraemia. *N Engl J Med* 1986;314:1535–42.

5 Anon. Antidepressant-induced hyponatraemia. *Curr Probl Pharmacovigilance* 1994;20:5–6.

6 Liu BA, Mittman N, Knowles SR, Shear NH. Hyponatraemia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *Can Med Assoc J* 1996;155:519–27.