Reminder of important clinical lesson

Unusual case of hyponatraemia

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Summary

Hyponatraemia is the most common electrolyte abnormality, encountered in up to 30% of inpatients. Inappropriate management can have serious implications for patients; including demyelinating disease, coma and death. We have used a case report to identify the common problems, and provide useful strategies in management for which these can be avoided. The aim was to provide a framework which clinicians can adopt, in order to improve clinical practice and provide optimum outcome for the patient.

BACKGROUND

This case demonstrates possible errors and delay in managing hyponatraemia, and also provides a means of learning how to avoid this. Without effective understanding of the principles behind fluid balance in relation to plasma sodium, the management of such cases can be very difficult, especially for junior clinicians.^{1–4}

CASE PRESENTATION

An 83-year-old man was brought into hospital by ambulance after a collapse at home during the night. This was followed by a brief period of loss of consciousness. He has a history of benign prostatic hyperplasia; hypertension; and atrial fibrillation. He had been taking the following medications: Bisoprolol 2.5 mg once in a day, Lisinopril 10 mg once in a day, Simvastatin 40 mg once at night, Tamsulosin 400 mcg once in a day and warfarin.

This was his second collapse in 3 days, in the first of which he sustained a head injury but did not present to hospital. On admission his lying blood pressure was 120/70 mm Hg; he was confused and unable to get out of bed. Neurological examination revealed a Glasgow Coma Scale of 11, but no other neurological abnormalities. Fundus examination was normal. A CT head done on admission revealed 'a large rounded lesion in the region of the pituitary gland, with no midline shift'. The lesion was thought to be most likely that of a pituitary adenoma and an MRI scan was requested to further assess the lesion. The MR scan revealed a sizeable pituitary fossa mass with superior and anterior extension into the suprasellar region, with posterior displacement of the optic chiasm. There was no

evidence of any acute bleed within the pituitary tumour; which from the radiological findings was thought to be a macroadenoma. Surprisingly, clinical examination of the visual fields by confrontation was normal. The patient was referred to the endocrinology department and further endocrine investigations were subsequently arranged, including urinary sodium, with urine and plasma osmolalities (table 1).

DIFFERENTIAL DIAGNOSIS

With the above investigations, a diagnosis of syndrome of inappropriate anti-diuretic hormone (SIADH) was made.

TREATMENT

The patient was clinically euvolaemic; however, initial attempts of management included placing the patient on an intravenous fluid regime of normal saline. The sodium dropped from 128 mmol/l on admission to 122 mmol/l after a few days. The patient was fluid restricted to 1 litre a day and a course of 50 mcg Fludrocortisone was started. The plasma sodium increased only minimally, and after being reviewed by the endocrinologist, Fludrocortisone was discontinued and the patient was started on 15 mg Tolvaptan—a vasopressin receptor one antagonist. His sodium levels were checked regularly thereafter and the effects are demonstrated in table 2 and figure 1.

Following admission the plasma sodium level dropped from 128 to 122 mmol/l.

Once the patient was subsequently started on a fluid restriction, there was an initial rise in plasma sodium from 122 to 125 mmol/l; however, this plateaued over the

Table 1 Initial investigations and results

Urea and electrolytes		Screening for SIADH		Further endocrine tests (9:00)	
Na ⁺	125 mmol/l	Urinary sodium	52 mmol/l	Cortisol	394 nmol/l
K ⁺	3.7 mmol/l	Urine Osmolality	708 mos ml/kg	30 min postsynacthen cortisol	588 nmol/l
Urea	3.8 mmol/l	Plasma Osmolality	269 mos ml/kg	Thyroid-stimulating hormone (TSH)	1.88 mu/l
Creatinine	74 umol/l			Testosterone	2.3 nmol/l
Glucose	6.6 mmol/l			Prolactin	130 mu/l

Table 2 Monitoring of plasma electrolytes

Timeline	Na ⁺ (mmol/l)	K ⁺ (mmol/l)
Before commencing on Tolvaptan		
On admission	128	3.7
Day 5	122	4.4
Day 10	125	3.8
Day 20	125	3.9
While on Tolvaptan		
Day 21 (after 24 h Tolvaptan)	132	3.7
Day 25	132	3.8
Day 30	136	3.7
Day 35	125	3.3
Day 40	136	3.7
Day 45	135	3.5
Day 50	138	3.8

following week showing no signs of improvement or any change in his clinical status. After starting Tolvaptan treatment the sodium was driven towards the 'normal range' and was maintained between 132 and 138 mmol/l. The patient had improved clinically and was now able to safely get out of bed and feed himself, which was not possible previously.

After 2 weeks, Tolvaptan was stopped for 72 h (days 33–35) to assess whether the patient could maintain his plasma sodium without medication. However, the plasma sodium dropped to 125 mmol/l 24 h after Tolvaptan was discontinued and there was clinical deterioration. He was therefore restarted on Tolvaptan.

OUTCOME AND FOLLOW-UP

The patient was discharged home on Tolvaptan once his serum sodium levels had stabilised to around 138 mmol/l. He was still suffering from symptoms of a constant dry mouth and increased thirst which he finds problematic, both being recognised side effects of Tolvaptan in addition to constipation and urinary frequency. Follow-up was arranged with the neurosurgeons who decided to manage the patient via endoscopic transsphenoidal resection of the pituitary. Samples from the lesion were sent to be analysed and the histology has shown a follicle-stimulating hormone (FSH) staining macroadenoma.

The patient recovered well postoperatively and did not develop any evidence of SIADH despite discontinuing Tolvaptan postoperatively. His serum sodium levels were

Figure 1 A line graph to demonstrate the changes in this patient's plasma sodium levels.

maintained between 136 and 138 mmol/l. He was discharged on replacement of Hydrocortisone: 10 mg in the morning, 5 mg in the afternoon and evening, and the patient is doing well.

DISCUSSION

This case demonstrates the need to have an appropriate understanding of both the chronology and the fluid status in patients with hyponatraemia. A flowchart constructed to use in the majority of cases of true hyponatraemia, irrespective of the diagnosis has been shown in figure 2. However, it should be noted that the main focus of treatment should be the correction of the underlying cause.

The first step should be to check for any easily reversible causes. This includes screening for any iatrogenic causes (especially if the patient is on diuretic therapy), or metabolic causes including hypothyroidism, hyperglycaemia or hyperlipidaemia (pseudohyponatraemia).

Acute hyponatraemia

Patients with a severe drop in plasma sodium (ie, <125 mmol/l occurring within 48 h) typically present with severe neurological signs or symptoms. This may manifest as seizures, stupor or coma. It has therefore been suggested that for patients in which the timeline of severe hyponatraemia is unknown (eg, an acute admission), but have neurological signs or symptoms without a more likely cause, it should be assumed that their hyponatraemia is an acute episode.⁵

Acute hyponatraemia should be managed with boluses of hypertonic saline solution.

This condition is serious, and senior doctors should be involved. A decision may need to be made on whether to transfer these patients to a high-dependency unit.

Chronic hyponatraemia

Chronic hyponatraemia is defined as having lasted >48 h with no signs of cerebral oedema. For these patients or those with an acute non-severe hyponatraemia; the optimum treatment depends on hydration status.

Hypovolaemic hyponatraemia

In this cohort of patients, the direct cause is fluid loss. The treatment therefore consists of fluid replacement; normal saline usually being the appropriate choice. If the patient is on any diuretics they should be stopped, reduced or changed. If there is no obvious cause from the history or medication list, Addison's disease should be considered and patients should have a short Synacthen test.

Euvolaemic/hypervolaemic hyponatraemia

For these patients, the focus of treatment is to create a negative fluid balance. They should be placed on a fluid restriction: 1 litre per day being the accepted norm. The idea is to ensure that they are in negative fluid balance, that is, oral fluid intake is less than total urine output plus insensible losses per 24 h.^{1 2} Good clinical practice includes keeping an accurate record of fluid balance for such patients.

These patients should be investigated for SIADH by measuring urinary sodium with urine and plasma osmolality. Blood and urine samples should be collected as close together in time as possible.

Figure 2 Flowchart for severe hyponatraemia.

The addition of diuretics may be indicated for patients who are in fluid overload. This includes patients with cirrhosis, nephrotic syndrome or congestive cardiac failure.

SIADH

The syndrome of inappropriate antidiuretic hormone secretion is the most common cause of euvolaemic hyponatraemia.⁶ SIADH involves the overproduction of vasopressin (antidiuretic hormone) from either the posterior pituitary gland or an ectopic source such as a malignancy or central nervous system (CNS) disease.⁷ Also, drugs such as nicotine, morphine, tolbutamide or antidepressants can cause an elevated vasopressin secretion.² Vasopressin works by increasing the permeability of the distal tubules and collecting ducts in the kidney, leading to increased water reabsorption thus lowering plasma

osmolality. Any attempt to correct the sodium levels of these patients with normal saline may cause a severe worsening of hyponatraemia by adding to the availability of water to be reabsorbed, and further diluting the plasma.

The diagnosis of SIADH can only be made with a low plasma osmolality, high urinary osmolality and urinary sodium; with a euvolaemic patient. Cerebral salt wasting syndrome (CSWS) is caused by an elevation in natriuretic peptides following acute brain injury, and can mimic the osmolality and urinary sodium results of SIADH. CSWS is commonly misdiagnosed as SIADH.⁴ However, patients with CSWS are hypovolaemic. This underlines the importance of an appreciation of the fluid status of patients. SIADH can only be diagnosed in the presence of normal thyroid and adrenal function.^{1 2} However, it should be noted that ill patients often suffer from 'sick

euthyroid syndrome' which would not be a cause of hyponatraemia.

There are currently no standard reference values for urinary sodium being considered 'high' for diagnosing SIADH.⁶ This can lead to discrepancies between different clinicians and misclassification of patients with hyponatraemia. This is especially true for patients with 'borderline' values of urinary sodium. For the purpose of this study, and the corresponding algorithm, we have defined a urinary sodium of >40 mmol/l as being 'high' and together with a raised plasma osmolality; indicative of SIADH. We have chosen this value as this corresponds to the value used by the endocrinologists within this Hospital, and many of the study references used.² However, it should be noted that this should still be used in correlation with a high urine osmolality, commonly defined as >100 mmol/kg.^{2 3 5}

Fluid restriction to 0.5–1 litre per day is the first-line treatment for hyponatraemia associated with SIADH. This may cause compliance issues in some patients, especially if this form of treatment is intended to be long term. In some patients, the extent of hyponatraemia and elevated vasopressin may be too severe to be managed by fluid restriction alone. It is for these patients that alternatives are needed. Demeclocycline, a tetracycline antibiotic, as a side effect has vasopressin antagonistic properties, and has been used for years to treat SIADH. However, tetracyclines are discouraged for patients in renal failure. Furthermore, increased use of an antibiotic for this purpose may be seen as inappropriate as bacterial resistance is becoming increasingly more common. Lithium is another medication that has shown vasopressin antagonistic side effects. However, lithium only causes a mild increase in plasma sodium, and is associated with an impressive array of side effects and problems with toxicity.^{8 9}

Within the past few years there has been increased interest in the 'vaptan' group of vasopressin antagonists. Tolvaptan is currently the only licensed drug of this class in Europe and works as a competitive vasopressin receptor two antagonist, indicated to treat hyponatraemia in patients with SIADH. In the USA it is also licensed and used to treat hyponatraemia associated with congestive cardiac failure (CCF), or cirrhosis (ie, any dilutional hyponatraemia).

Vaptans may cause a rapid correction of hyponatraemia and therefore a low dose should be selected when initiating treatment, with serum sodium measurements at least once per day. Trials from 2004 showed Tolvaptan was successful in improving sodium levels, while promoting the excretion of excessive fluids without causing hypotension, hypokalaemia or affecting kidney function.^{10 11} This is the significant difference with using a vasopressin antagonist rather than a synthetic corticosteroid such as Fludrocortisone, which has well-documented side effects including hypokalaemia, with water retention and hypertension.

Osmotic Demyelinating Syndrome

Rapid correction of chronic hyponatraemia would create a hypertonic extra-cellular fluid compartment, causing rapid water loss from brain cells. This leads to demyelination within the CNS, affecting the pons especially and may

cause an irreversible 'locked-in' syndrome with paralysis of all skeletal muscles below the face.¹²

There is a serious risk of osmotic demyelinating syndrome (ODS) occurring for rises of plasma sodium >12 mmol/l per day. The general recommendation is to aim for a rise of no more than 8 mmol/l in 24 h. It would be wise to measure sodium levels twice daily when starting any medication which may increase sodium quickly.

As seen in the case history, sodium levels rise quickly within 24–48 h of starting Tolvaptan. Also, levels can fall just as quickly once the medication is discontinued. A dose of 15 mg produced the recommended rise of plasma sodium of approximately 7–8 mmol/l.

Learning points

- Hyponatraemia has a multifactorial range of causes, the most common being syndrome of inappropriate anti-diuretic hormone and diuretic therapy. The managements for these two examples are distinctly different, and without a correct diagnostic workup there is a risk of mismanagement.
- A case control study of over 100 inpatients with severe hyponatraemia showed 73% of cases having no documented explanation of the cause.
- However, 50% of patients had a further drop in sodium during the course of treatment with fluid restriction, as happened in our patient.
- Many patients are not investigated fully and this study showed only 47% of patients had urine osmolalities measured, 40% had urinary sodium measurements and only 15% had any investigation of adrenal function.¹³
- Hyponatraemia is a serious and potentially life-threatening condition that occurs frequently in hospitalised patients. For this reason, the correct clinical workup and management should be done.
- This can be achieved with an appreciation of the role of the hydration status; and with a systematic approach to the required clinical investigations.
- Additionally, the potential of causing osmotic demyelinating syndrome from the rapid correction of sodium should always be kept in the mind of the treating clinician.

Competing interests None.

Patient consent Obtained.

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