Novel treatment (new drug/intervention; established drug/procedure in new situation)

Preventing overcorrection of hyponatraemia with desmopressin

Sophie Claire Tomlin,¹ Ruth Williams,² Steve Riley³

¹East Wandsworth Older Adults CMHT, Springfield Hospital, London, UK;

²Department of Respiratory Medicine, Glan Clwyd Hospital, Rhyl, UK;

³Institute of Nephrology, University Hospital of Wales, Cardiff, UK

Correspondence to Dr Sophie Claire Tomlin, sophie_tomlin@hotmail.com

Summary

A 61-year-old woman was admitted with history of vomiting, diarrhoea and severe hyponatraemia (Na^+ 109). The cause of the hyponatraemia was due to intravascular volume depletion resulting in a non-osmotic release of antidiuretic hormone (ADH) with the added effects of a thiazide diuretic. She was also on fluoxetine which may induce inappropriate secretion of ADH. Despite cautious fluid replacement, the patient's serum sodium increased by 12 mmol/l over the first 18 h (and by 10 mmol/l over 12 h). This trajectory, coupled with the rapid decrease in urine osmolality, suggested that this patient was at risk of significant brain injury due to rapid correction of serum sodium. The use of desmopressin slowed the rise in serum sodium allowing brain adaptive mechanisms time to protect against osmotic demyelination.

BACKGROUND

Hyponatraemia is the most common electrolyte abnormality, and has an increased frequency in females and hospitalised patients, although its incidence will depend on the patient population.¹ Hyponatraemia signifies relative excess of water in relation to sodium, and can be defined as a serum sodium level of less than 135 meq/l (and considered severe when the level is less than 125 meq/l). It may present as a chronic hyponatraemia, where levels drop over weeks to months and as such symptoms and complications are typically moderate, or as acute hyponatraemia caused by a rapid fall in sodium with potentially significant complications including cerebral oedema. In the setting of the brain volume returning to normal, rapid correction of severe hyponatraemia can result in osmotic demyelination, which often causes an irreversible neurological insult.²

The association between hyponatraemia and mortality has been established by several studies however the causality has been more difficult to prove.³ A recent editorial proposed three possible scenarios to explain this increased mortality. In the first, hyponatraemia is a direct cause of death (ie, in osmotic demyelination syndrome). In the second scenario, hyponatraemia is an epiphenomenon of the underlying disease, and it is this underlying condition that is responsible for death. The third scenario proposed is that hyponatraemia causes organ dysfunction and indirectly contributes to mortality.³ A formulaic approach to the clinical management of hyponatraemia is not possible but requires clinicians to decide on the cause and then implement treatment with close monitoring. We describe a case in which this close monitoring resulted in an ability to alter management and avoid potentially serious sequelae.

CASE PRESENTATION

A 61-year-old woman was admitted with a 1 week history of vomiting and diarrhoea, and an 8 h history of confusion

and fever. She had a medical history of irritable bowel syndrome, reflux oesophagitis, hypertension, hypercholesterolaemia and osteoarthritis. Her medications were bendroflumethiazide 2.5 mg once daily (OD), rosuvastatin 20 mg OD, ramipril 5 mg OD, mebeverine 200 mg OD, fluoxetine 20 mg OD and omeprazole 20 mg OD. Detailed examination was unremarkable with no evidence of a focal neurological deficit. Although blood pressure was 137/88, and the pulse rate was 76 beats per min, the patient was clinically intravascularly depleted. This was supported by small volume and concentrated urine.

On admission, her bloods showed a marked hyponatraemia (Na^+ 109) and hypokalaemia (K^+ 2.8). Unfortunately serum and urine osmolality were not done on admission. However at 12 h, serum osmolality was 233 mOsm/kg confirming a true hyponatraemia.

The working diagnosis of the hyponatraemia was that of intravascular volume depletion resulting in a non-osmotic release of antidiuretic hormone (ADH), the cause of this being due to vomiting and diarrhoea (also adding to electrolyte losses) and the effects of the thiazide diuretic. The patient was also on fluoxetine, which can induce inappropriate ADH secretion.

Fluid replacement with normal saline was initiated and the diuretic discontinued. Three litres of 0.9% sodium chloride were administered and the patient's serum sodium increased by 12 mmol/l over the first 18 h (and by 10 mmol/l over 12 h). At this point, the patient's urine osmolality was 86 mOsm/kg and urinary sodium was <20 mmol/l.

DIFFERENTIAL DIAGNOSIS

At this stage, it was felt that the volume correction had turned off her endogenous ADH thus resulting in the rapid correction of the hyponatraemia as the kidney was able to excrete the excess water. This was supported by a sudden increase in the output of dilute urine by the patient.

Figure 1 Graph demonstrating effect of desmopressin on rate of correction of hyponatraemia.

TREATMENT

Studies suggest that patients with a rate of correction of 20 mmol/l in 24 h are the most likely to develop significant brain injury.^{4–6} Current recommendations suggest a maximum correction rate of the sodium level of 10–12 mmol/l in the first 24 h; the usual advised goal for correction being 8 mmol/l/day in patients at risk of neurological complications. The trajectory of the sodium increase coupled with the marked decrease in urine osmolality suggested that this patient was at risk of significant brain injury if left unchecked. Therefore we opted to give desmopressin to slow the rise in serum sodium allowing brain adaptive mechanisms time to protect against such injury.

At this point 25 h after admission, the serum sodium was 121 mmol/l and the patient was given 3 micrograms of DDAVP with a 400 ml bolus of 5% dextrose (based on 6 ml/kg body weight). Two hours later, the serum sodium had dropped to 115 mmol/l (figure 1). The sodium did not decrease any further, and 16 h later the sodium was 118 mmol with a urine osmolality of 330 mOsm/kg, suggesting that the ADH was still acting but that the hyponatraemia was slowly improving.

OUTCOME AND FOLLOW-UP

Fluid restriction was continued, and 24 h later, the Na was 126 and the patient was discharged. Subsequent outpatient follow-up revealed a normal serum sodium.

DISCUSSION

The majority of cases of hyponatraemia are due to impaired water excretion as a result of advanced kidney disease, the persistent release of ADH induced by either true or effective volume depletion, the syndrome of inappropriate ADH secretion, medications including thiazide diuretics and or hypothyroidism.¹

The symptoms associated with hyponatraemia include nausea and vomiting, lethargy, anorexia, confusion, seizures, coma and death. The severity and nature of symptoms is associated with the level of sodium, with lower levels correlating with increased morbidity and mortality, however there is emerging data that even mild hyponatraemia may be the cause of multiple complications and undiagnosed symptoms.²

As a consequence of the falling serum osmolality, there is osmotic water movement into the brain. The brain will make adaptations to normalise brain volume, however, if the hyponatraemia is acute in onset it can lead to significant and symptomatic cerebral oedema. In the setting of the brain volume returning to normal, rapid correction of severe hyponatraemia can result in osmotic demyelination, which often causes an irreversible neurological insult.^{4–7} Osmotic demyelination syndrome primarily occurs in over correction of severe hyponatraemia that has been present for at least 2 days (the time required for cerebral adaptations to occur); however, certain patients are at high risk even at higher serum levels and lower rates of correction.

A number of risk factors for demyelination have been identified but the most important appears to be the rate of correction. Studies have suggested that patients with severe hyponatraemia (for at least 2 days) whose serum sodium levels are raised more than 20 meq/l in the first 24 h or are overcorrected to above 140 meq/l, are at greatest risk of developing significant brain injury.^{4–6} Overcorrection of serum sodium may arise either as a direct response to the treatment given (for example the use of hypertonic saline) or from the restoration of the ability to suppress ADH release and as a result excrete maximally dilute urine. This phenomenon may be associated with rises in serum sodium of greater than 2 meq/l an hour.^{8–10} The failure of clinicians to recognise intravascular fluid depletion as contributing to the hyponatraemia can lead to inadvertent rapid rises in serum sodium purely from volume replacement.

Preventing overcorrection of serum sodium levels is vital, as there is no proven treatment for osmotic demyelination syndrome, and requires careful and frequent monitoring of levels. When managing patients who are developing overcorrection, it is useful to note that there is evidence in rats that partially reversing this is associated with improved neurological outcomes.^{9–11} It has been shown to be more effective in preventing neurological impairment than the use of steroid therapy.¹¹

Desmopressin (DDAVP) has been shown to be effective in preventing and reversing inadvertent overcorrection of hyponatraemia,¹² and current evidence therefore, supports its use in clinical practice.^{2–12–13} Desmopressin is a synthetic form of vasopressin, which acts by binding to the V2 receptors on the collecting ducts in the kidney to

increase water reabsorption, which results in dilution of serum sodium.

The regime used depends on whether the patient is within the 24 h limit of a rise of 10 meq/l but is correcting their serum sodium too rapidly (the aim being to slow down correction), or if they have exceeded the 24 h increase limit, the aim of intervention should be to re-lower the serum sodium, again using desmopressin. The preventive use of desmopressin is advisable in patients at high risk of overcorrection that is, when the hyponatraemia has been caused by inappropriate ADH secretion as a result of hypovolaemia, thiazide diuretics, antidepressants, very low dietary sodium intake or cortisol deficiency.

Learning points

- ▶ Hyponatraemia is the most common electrolyte abnormality, and has an increased frequency in females and hospitalised patients, although its incidence will depend on the patient population.¹
- ▶ Severe hyponatraemia requires careful and frequent monitoring of levels as rapid correction can result in osmotic demyelination, which often causes an irreversible neurological insult.
- ▶ Desmopressin (DDAVP) has been shown to be effective in preventing and reversing inadvertent overcorrection of hyponatraemia,¹² and current evidence therefore supports its use in clinical practice.^{2 12 13}

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Schrier RW.** Does 'asymptomatic hyponatremia' exist? *Nat Rev Nephrol* 2010;**6**:185.
2. **Sterns RH.** Osmotic demyelination syndrome and overly rapid correction of hyponatraemia. *UpToDate* **18**:2010.
3. **Hoorn EJ, Zietse R.** Hyponatremia and mortality: how innocent is the bystander? *Clin J Am Soc Nephrol* 2011;**6**:951–3.
4. **Sterns RH.** Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. *Ann Intern Med* 1987;**107**:656–64.
5. **Berl T.** Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int* 1990;**37**:1007.
6. **Karp BI, Laureno R.** Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine (Baltimore)* 1993;**72**:359.
7. **Sterns RH, Cappuccino JD, Silver SM, et al.** Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol* 1994;**4**:1522–30.
8. **Mohmand HK, Issa D, Ahmad Z, et al.** Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. *Clin J Am Soc Nephrol* 2007;**2**:1110–7.
9. **Soupart A, Penninckx R, Crenier L, et al.** Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering. *Kidney Int* 1994;**45**:193–200.
10. **Pham PC, Chen PV, Pham PT.** Overcorrection of hyponatremia: where do we go wrong? *Am J Kidney Dis* 2000;**36**:E12.
11. **Gankam Kengne F, Soupart A, Pochet R, et al.** Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int* 2009;**76**:614–21.
12. **Perianayagam A, Sterns RH, Silver SM, et al.** DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 2008;**3**:331–3.
13. **Sterns RH, Hix JK.** Overcorrection of hyponatremia is a medical emergency. *Kidney Int* 2009;**76**:587–9.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Tomlin SC, Williams R, Riley S. Preventing overcorrection of hyponatraemia with desmopressin. *BMJ Case Reports* 2011;**10**:1136/bcr.07.2011.4512, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow