The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences

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Abstract

Hyponatraemia is the commonest electrolyte abnormality found in hospital inpatients, and is associated with a greatly increased morbidity and mortality. The syndrome of inappropriate antidiuretic hormone (SIADH) is the most frequent cause of hyponatraemia in hospital inpatients. SIADH is the clinical and biochemical manifestation of a wide range of disease processes, and every case warrants investigation of the underlying cause. In this review, we will examine the prevalence, pathophysiology, clinical characteristics and clinical consequences of hyponatraemia due to SIADH.

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Introduction

Hyponatraemia is by far the most common electrolyte imbalance found in hospital inpatients (1), and severe hyponatraemia has been detected in 1% of hospital inpatients, with higher prevalence rates in the elderly (2). This is a clinically significant statistic, given that patients with symptomatic hyponatraemia have a vastly increased mortality when compared with normonatraemic controls (3). Hyponatraemia has many different pathophysiological causes, each of which needs to be managed differently, making accurate diagnosis essential to enable the commencement of therapy to reduce morbidity and mortality. The most common cause of hyponatraemia in hospital inpatients is syndrome of inappropriate antidiuretic (SIADH), which has a wide range of causes. In this review, we will discuss the prevalence, symptoms, signs and consequences of hyponatraemia due to SIADH.

Prevalence of hyponatraemia

Hyponatraemia is relatively common in ambulatory patients. A Belgian study reported that the prevalence of mild hyponatraemia (<135 mmol/l) was 4% in a randomly selected control group of healthy elderly patients (4), whereas the population-based Copenhagen Holter study showed a higher prevalence of 11%, using a slightly higher cut-off of 137 mmol/l (5). However, the incidence of new hyponatraemia in hospitalised patients is significantly higher. A large study of 7965 patients with pneumonia showed that 8% developed hyponatraemia during the course of hospital admission (6). Our own data show that 56% of the patients admitted with subarachnoid haemorrhage develop hyponatraemia, with 20% developing clinically significant drops in plasma sodium concentration to <125 mmol/l (7). Significant rates of hyponatraemia of between 10 and 20% also occurred in patients admitted to neurosurgical units with intracranial tumours and haematomas, and in patients undergoing pituitary surgery (8).

The almost universal finding in all cross-sectional studies of patients with hyponatraemia is the increased mortality in patients with low plasma sodium concentrations. Gill's study of hospitalised patients with plasma sodium concentration <125 mmol/l showed an overall mortality of 28%, which is significantly higher than that in eunatraemic controls (9%) (9). However, this study also showed a clear gradation of risk of death according to the severity of hyponatraemia, with mortality of 50% in patients with plasma sodium concentrations <115 mmol/l. Clayton's study of patients with severe hyponatraemia (<125 mmol/l) showed that the excess mortality in this group extends beyond the time frame of hospital admission, with a mortality of 20% in hospital and 45% within 6 months of follow-up (10). The high mortality in this study was attributed to the mortality associated with the illnesses which precipitated hyponatraemia, such as cardiac failure, liver disease and small cell carcinoma of the lung. However, a role for hyponatraemia itself was suggested by a Dutch paper, which reported higher mortality rates in hyponatraemic patients who did not

receive specific treatment for hyponatraemia compared with those who did (37 vs 13%) (11). These data strongly suggest that hyponatraemia should not be therapeutically ignored, even if the underlying disease process is serious.

Interestingly, published data obtained from cohorts of patients with milder hyponatraemia (<137 mmol/l) suggest that excess mortality is not confined to patients with plasma sodium concentration <125 mmol/l. Patients with mild hyponatraemia in the community (4) and with pneumonia (6), and those in intensive care (12) have all been shown to have excess mortality compared with patients with normal plasma sodium concentrations. One of the most comprehensive studies of mortality and hyponatraemia is a recently published prospective cohort study of 98 411 patients hospitalised at two Boston teaching hospitals between 2000 and 2003 (13). The authors documented hyponatraemia (<135 mmol/l) in 14.5% of the patients on admission, and they were able to demonstrate that hyponatraemia increased mortality at 1 and 5 years. The risk of death was apparent even in those with mild hyponatraemia (130–134 mmol/l, hazard ratio 1.38). The large study population lent considerable power to the statistical evaluation, and the data provided conclusive evidence that mild hyponatraemia is potentially more sinister than previously considered. Data from these recent publications have re-opened the debate about the potential deleterious effects of mild hyponatraemia, which has traditionally been regarded as being asymptomatic and which does not warrant therapeutic intervention.

The data from papers cited so far have derived from generic studies of hyponatraemia, rather than from those specifically devoted to SIADH, so the relevance and implication for SIADH are assumed rather than proven. Some studies undoubtedly described a majority of patients with SIADH (7, 10), but as many were retrospective, classical diagnostic criteria had not been applied, and the number with true SIADH was ill defined. In all studies of hyponatraemia, a significant number also have multifactorial hyponatraemia. What is clear from the prevalence data is that hyponatraemia is common, the commonest cause of hyponatraemia is SIADH and hyponatraemia due to all causes increases mortality.

Hyponatraemia due to SIADH

The first step in the diagnosis of SIADH is to differentiate it from other causes of hyponatraemia. There are a number of classifications of the pathogenesis of hyponatraemia. Some authorities have suggested a classification based on whether hyponatraemia is dilutional, depletional or redistributional in nature (14). This method has the merit of dividing hyponatraemia on pathophysiological criteria. In routine clinical practice, we have adopted a pragmatic approach to hyponatraemia, in which classification of causation is based on clinical and biochemical estimation of extracellular volume status. This divides hyponatraemia into hypovolaemic, euvolaemic and hypervolaemic aetiologies (see Table 1). The advantage in our experience is that this classification is easily understood by practitioners who are not experts in hyponatraemia. Although the clinical featues of the three categories are quite distinct, in practice, it can be difficult to distinguish mild hypovolaemia from euvolaemia. As can be seen in Table 1, the causes of hyponatraemia are quite diverse, and so, accurate diagnosis is essential to enable correct management. Hypovolaemic hyponatraemia can be difficult to diagnose, as serum urea may be low in hypovolaemic elderly patients and urinary sodium may be low in SIADH due to anorexia. In these cases, an isotonic saline infusion can be helpful. It has been shown that patients diagnosed with SIADH whose urinary osmolality is <500 mosmol/kg raise their plasma sodium in response to isotonic saline infusion (15).

Euvolaemic hyponatraemia is the commonest cause of hyponatraemia in hospitalised patients. Although experimental models of SIADH show that blood volume is slightly expanded in SIADH (16), with suppression of

Table 1 Causes of hyponatraemia.

	Clinical signs	Urinary Na$^+$ <20 mmol/l	Urinary Na$^+$ >40 mmol/l
Hypovolaemic	Dry mucous membranes Decreased turgor Tachycardia Hypotension (orthostatic) Raised urea, rennin	GI losses Mucosal losses Pancreatitis Sodium depletion post diuretics	Diuretics Addison's disease Cerebral salt wasting Salt wasting nephropathy
Euvolaemic	Underlying illness	Hypothyroidism SIADH with ongoing fluid restriction Primary polydipsia Inappropriate fluid replacement	SIADH ACTH deficiency
Hypervolaemic	Peripheral oedema Ascites Raised JVP Pulmonary oedema Underlying illness	Cirrhosis Cardiac failure Nephrotic syndrome	Cardiac failure or cirrhosis on diuretic therapy

JVP, jugular venous pressure.

plasma renin and elevation of plasma natriuretic peptides, the expanded extracellular volume is not detectable clinically and does not cause oedema. SIADH is therefore classified as euvolaemic hyponatraemia. SIADH needs to be distinguished from other causes of euvolaemic hyponatraemia, such as inappropriate hypotonic fluid replacement, particularly in patients following surgery. Hyponatraemia has also been reported to occur as a direct result of surgical procedures; for example, bladder irrigation with hypotonic solutions during transurethral resection of the prostate gland can lead to direct absorption of water from the bladder, producing euvolaemic dilutional hyponatraemia (17, 18). Euvolaemic hyponatraemia may also occur due to inappropriate fluid replacement after exercise (19) or diarrhoeal illness.

An important cause of euvolaemic hyponatraemia, which must be excluded before the diagnosis of SIADH can be made, is ACTH deficiency. In contrast to Addison's disease, which is characterised by both glucocorticoid and aldosterone deficiencies, ACTH deficiency is manifested by cortisol deficiency but not by aldosterone deficiency. Cortisol is necessary for efficent excretion of free water (20), and glucocorticoid deficiency is associated with retention of free water and development of hyponatraemia with a biochemical picture identical to SIADH. Patients with ACTH/cortisol deficiency and hyponatraemia have elevated plasma arginine vasopressin (AVP) concentrations, which further contribute to the tubular reabsorption of water (21). Glucocorticoid therapy has been shown to suppress AVP secretion (22), which allows the excretion of free water and the normalisation of plasma sodium concentrations in patients with ACTH deficiency (21). Diagnosis can be aided by the fact that patients with ACTH deficiency have a lower serum bicarbonate and aldosterone concentration than those with SIADH (23).

The distinction between true SIADH and the hyponatraemia associated with ACTH/cortisol deficiency is particularly important in patients with neurosurgical conditions, who commonly develop hyponatraemia (8). Over 50% of the patients with acute subarachnoid haemorrhage develop hyponatraemia, most of which has been attributed to SIADH (7). However, data have shown that a significant minority of long-term survivors of traumatic subarachnoid haemorrhage have evidence of permanent ACTH deficiency (24). The possibility that some of the hyponatraemia attributed in the immediate post-haemorrhage period to SIADH actually reflects acute ACTH deficiency remains unproven. However, 16% of the patients with acute traumatic brain injury develop ACTH deficiency (25), and some of these patients develop very severe hyponatraemia (26). We have adopted a policy of routine inclusion of measurement of cortisol at 0900 h in all patients with apparent SIADH due to neurosurgical conditions such as traumatic brain injury, subarachnoid haemorrhage, subdural haematoma and intracranial haemorrhage,

and commencing empirical treatment with glucocorticoids if the reading is inappropriately low for the degree of expected stress–response ($<$ 300 nmol/l, and between 300 and 500 nmol/l if clinical suspicion is high). We have identified a significant number of patients with severe ACTH deficiency secondary to pituitary trauma as a result. Important clinical clues that neurosurgical patients with apparent SIADH may have acute ACTH deficiency include the presence of hypoglycaemia or hypotension, particularly when the latter is resistant to pressor agents.

SIADH is a clinical manifestation of a wide range of clinical disorders and drug therapies, and is the most common cause of euvolaemic hyponatraemia in modern clinical practice. A variety of clinical disorders can cause inappropriately increased AVP secretion, leading to inappropriate water retention and consequent hyponatraemia. The diagnostic criteria for SIADH are outlined in Table 2. Two supplementary criteria also exist – the direct measurement of a high AVP level and the measurement of urine excretion following administration of a water load. However, these are not often useful; RIAs with good enough antibodies to AVP to give meaningful results are not widely available, and the results take weeks to become available. The administration of a water load, which can worsen hyponatraemia significantly, should only be used in specialised units with experience of this investigation. The minimum information required for the diagnosis of SIADH is hyponatraemia in a euvolaemic patient with inappropriately concentrated urine, and the exclusion of hypothyroidism and glucocorticoid deficiency. Older literature sometimes states that urine osmolality must exceed plasma osmolality for the diagnosis to be confirmed, but this is fallacious. If plasma osmolality is subnormal (i.e. below the osmotic threshold for AVP secretion), then plasma AVP levels should be suppressed, which should then allow a hypotonic diuresis with maximally hypotonic urine ($<$ 100 mosmol/kg). Therefore, a urine osmolality of more than 100 mosmol/kg in a patient in whom AVP levels should be suppressed indicates that inappropriate antidiuresis is in progress and is consistent with the diagnosis of SIADH. Many patients are erroneously diagnosed with SIADH due to incomplete or inadequate implementation of the above criteria, and additional tests may prove useful. The lower

Table 2 Diagnostic criteria for the diagnosis of SIADH.

1. Hypo-osmolality; plasma osmolality $<$ 280 mosmol/kg, or plasma sodium concentration $<$ 134 mmol/l
2. Inappropriate urinary concentration (Uosm $>$ 100 mosmol/kg) for hyponatraemia
3. Patient is clinically euvolaemic
4. Elevated urinary sodium ($>$ 40 mmol/l), with normal dietary salt and water intake
5. Exclusion of hypothyroidism, diuretics and glucocorticoid deficiency – particularly in patients with neurosurgical conditions

fractional excretion of uric acid found in SIADH can be used to distinguish it from diuretic-induced hyponatraemia, as serum urea is a less reliable marker of hydration status in the elderly (27). As discussed earlier, when compared with patients with hyponatraemia due to hypocortisolaemia, patients with SIADH have normal serum bicarbonate and potassium, and a lower anion gap (28).

Causes of SIADH

The most common causes of SIADH are malignancy, pulmonary disorders, CNS disorders and medication; these are summarised in Table 3. SIADH was originally described by Bartter & Schwartz in two patients with lung carcinoma, who had severe hyponatraemia at presentation (29). SIADH is quite common in patients with small cell carcinoma of the lung, and may be the presenting feature which instigates a search for the underlying tumour (30). Indeed, the link between

Table 3 Causes of SIADH.

Malignancy	Small cell lung cancer
	Nasopharyngeal cancer
	Mesothelioma
	GI tract malignancy
	Pancreatic malignancy
	GU tract malignancy
	Lymphoma
	Sarcoma
Drugs	*Desmopressin*
	Selective serotonin reuptake inhibitors
	Carbamazepine
	Prostaglandins
	Tricyclic antidepressants
	Phenothiazines
	Haloperidol
	3,4-Methylenedioxymethamphetamine
	Quinolones
	Levetiracetam
	Cyclophosphamide
	Vincristine
Pulmonary	Pneumonia, especially *Legionella* and *Mycoplasma*
	Tuberculosis
	Abscess
	Vasculitis
	Positive pressure ventilation
Intracranial pathology	Tumour
	Meningitis
	Encephalitis
	Abscess
	Vasculitis
	Subarachnoid haemorrhage
	Subdural haemorrhage
	Traumatic brain injury
Miscellaneous	Multiple sclerosis
	Guillain–Barre syndrome
	Acute intermittent porphyria
	HIV
	Idiopathic

malignant disease of various organs and SIADH is so strong that any patient presenting with SIADH and other suspicious symptoms such as weight loss should be thoroughly investigated for underlying malignancy.

The main pharmaceutical agents which have been implicated in the pathogenesis are the various groups of antidepressants; selective serotonin reuptake inhibitors (SSRIs) cause SIADH in between 0.5 and 32% of the patients, with hyponatraemia occurring most commonly in elderly female underweight patients who are also on diuretics (31). SIADH usually occurs in the first few weeks after SSRIs are introduced (32). Most drugs, including SSRIs, are thought to cause SIADH through stimulation of excess AVP secretion, although some may potentiate the effect of AVP at the level of the kidney. It has been estimated that 12% of the hospitalised patients on SSRI therapy develop SIADH (33). Many patients who are treated with these medications also have abnormally high thirst, which can give rise to very severe hyponatraemia when combined with SIADH. One important pharmaceutical cause of SIADH is 3,4-methylenedioxymethamphetamine (MDMA), which is an illegal recreational drug. The aetiology of MDMA-induced hyponatraemia is probably multifactorial, but it almost certainly causes inappropriate AVP secretion (34–36).

SIADH is also commonly associated with intracranial diseases, particularly traumatic brain injury (25, 37, 38), where almost all cases resolve spontaneously with recovery from brain injury. Over 50% of the patients with subarachnoid haemorrhage develop hyponatraemia in the first week following the bleed, and 70% are due to SIADH (7). SIADH also commonly occurs after hypophysectomy and after surgery for primary brain tumours.
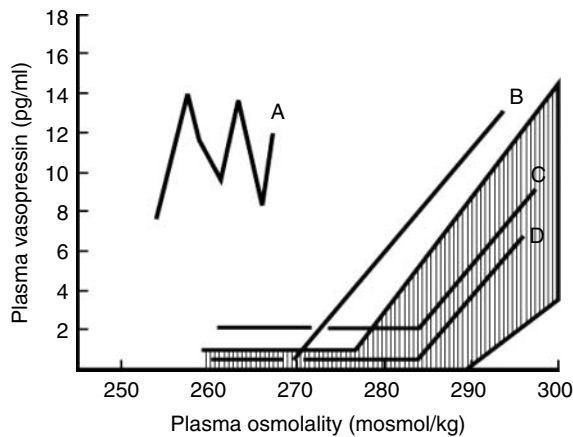
Classification of SIADH

SIADH occurs by definition when AVP secretion is not suppressed when plasma sodium concentration falls below the osmotic threshold for physiological AVP secretion (39). However, Zerbe *et al.* were able to utilise the measurement of plasma AVP with an early RIA to describe four different types of SIADH, defined by the pattern of AVP secretion across a range of plasma osmolalities (40) (Fig. 1):

i) Type A is the commonest form of SIADH. Some reports suggest that type A occurs in 40%, though our own experience suggests that type A is responsible for a much higher proportion of SIADH, at around 60–70%. Characteristically, type A patients exhibit excessive, random secretion of AVP, with loss of the close linear relationship between plasma osmolality and plasma AVP. Type A is common in lung cancer; *in vitro* studies have demonstrated that some lung

Figure 1 Summary of the four different patterns of AVP secretion in SIADH. Adapted with permission from Smith DM, McKenna K & Thompson CJ. Hyponatraemia. *Clinical Endocrinology* 2000 **52** 667–678.

tumours synthesise AVP (41), and that tumour tissue stains positive for AVP mRNA (42). Plasma AVP concentrations in type A SIADH are not suppressed physiologically by drinking (43), which makes patients vulnerable to the development of severe hyponatraemia. Studies have also demonstrated a lower osmotic threshold for thirst appreciation in this type of SIADH (43). This type of SIADH is also characteristic of nasopharyngeal tumours, which also stain positive for AVP mRNA.

ii) Type B is also common (20–40%). The osmotic threshold for AVP release is lowered – a 'reset osmostat' – such that secretion of AVP occurs at lower plasma osmolalities than normal. Because AVP is suppressed at plasma osmolalities below the lower, reset threshold, further overhydration leads to suppression of AVP release, which protects against the progression to severe hyponatraemia. Although most tumours manifest type A SIADH, some also present with type B SIADH, so the pattern of abnormal AVP secretion cannot be utilised to predict the causation of SIADH.

iii) Type C is a rare condition characterised by failure to suppress AVP secretion at plasma osmolalities below the osmotic threshold. Plasma AVP concentrations are thus inappropriately high at low plasma osmolalities, but there is a normal relationship between plasma osmolality and plasma AVP at physiological plasma osmolalities. This variant may be due to dysfunction of inhibitory neurones in the hypothalamus, leading to persistent low-grade basal AVP secretion (44).

iv) Type D is a rare clinical picture of SIADH with low or undetectable AVP levels and no detectable abnormality in circulating AVP response (45). It is thought that a nephrogenic SIADH (NSIAD) may be responsible for this picture (46). Gain-of-function mutations in the V2 receptor leading to a clinical

picture of SIADH, with undetectable AVP levels, have been described. The identified mutations had different nucleotide substitutions causing different levels of V2 receptor activation (46). This syndrome appears to be inherited in an X-linked manner, although heterozygous females may have varying degrees of inappropriate antidiuresis. Owing to variable expressivity of the gene involved, NSIAD may be clinically undetectable for years, until other contributing factors in later life lead to clinically significant hyponatraemia (47).

Although patients with SIADH have ambient plasma osmolalities which are below the physiological osmotic threshold for thirst, they continue to drink apparently normal fluid volumes (36); the reason for this is unknown. The parallel lowering of the thresholds for thirst and AVP release ensures the maintenance of fluid intake, predisposing to persistent hyponatraemia. However, hyponatraemia is often limited by 'escape from antidiuresis'. This protective homeostatic mechanism occurs when the kidney begins to increase the clearance of free water despite inappropriate plasma AVP concentrations (48). Initial natriuresis is followed by an increase in urine flow (49) with consequent water loss; this allows plasma sodium to stabilise and, occasionally, to rise. Although plasma sodium concentration does not usually rise into the normal physiological range during escape from antidiuresis, the development of severe hyponatraemia is prevented.

Studies in rat models of SIADH have demonstrated that the increase in water reabsorption is secondary to AVP-mediated expression of renal aquaporin 2 (50). A decrease in aquaporin 2 protein expression and V2 receptor binding capacity (51, 52) is thought to cause the renal resistance to AVP observed during escape from antidiuresis. Normally, AVP has long-term effects on aquaporin 2 via mRNA and protein expression, but it also has short-term effects via the V2 receptor, leading to increased cAMP. It is likely that this short-term AVP action is also altered in escape, since reduced levels of cAMP in the collecting ducts of rats with escape from antidiuresis have been demonstrated (53). This finding of reduced cAMP activity suggests that the short-term regulation of aquaporin activity by reduced vesicle 'shuttling' is also important in the development of 'escape from antidiuresis'.

Clinical consequences of hyponatraemia due to SIADH

The symptoms associated with hyponatraemia are varied, and are generally related to the severity of hyponatraemia, the rate of change in plasma sodium concentration, and the osmotic gradient between intracellular and extracellular fluids. Patients with mild hyponatraemia (plasma sodium concentration

>130 mmol/l) are traditionally regarded as asymptomatic, though the accompanying article in this supplementary issue of *European Journal of Endocrinology* will discuss data which challenge this assumption. At plasma sodium concentrations between 125 and 130 mmol/l, anorexia, nausea, vomiting and abdominal pain may develop. As plasma sodium concentration falls to between 115 and 125 mmol/l, agitation, confusion, hallucinations, incontinence and other neurological symptoms predominate. Hyponatraemia below 115 mmol/l may induce serious adverse neurological sequelae, such as seizures and coma, due to increased intracranial pressure. At this stage, hyponatraemia constitutes a medical emergency in need of urgent treatment. Although the main determinant of the symptoms experienced due to hyponatraemia is biochemical severity, symptoms are also more likely in the presence of other parameters, such as pyrexial illnesses, hypoxia and hypercapnia. If there is intracranial illness, space-occupying lesion or neurosurgical intervention, the onset of symptoms may occur at higher plasma sodium concentrations than usual.

The other main determinant of the onset or severity of symptoms is the rate of change in plasma sodium concentration. Symptoms are far more likely if the fall in plasma sodium is rapid, and tend to occur at higher plasma sodium concentrations. Chronic hyponatraemia may present as a relatively asymptomatic condition, even in cases where hyponatraemia is severe. In acute hyponatraemia, the main pathological consequence is the development of cerebral oedema, which may lead to raised intracranial pressure, cerebral herniation, hypoxia and even death (54). However, many patients with chronic hyponatraemia exhibit no apparent ill effects, despite severe biochemical hyponatraemia, due to the presence of cerebral adaptive mechanisms. The initial adaptive mechanism is the loss of intracerebral fluid, with depletion of sodium and potassium, to prevent cerebral oedema and gain of water (55). Later, glutamate, myo-inositol, *N*-acetylaspartate, aspartate, creatine, taurine, γ-aminobutyric acid and phosphoethanolamine are lost from the brain, further decreasing intracerebral osmolality (56). This allows equilibration with the osmolality of the plasma, preventing the development of cerebral oedema.

However, although these adaptive mechanisms serve to protect against cerebral oedema, chronic hyponatraemia is not entirely benign (57), as adaptation seems to fail in some patients, especially in post-menopausal women. Indeed, in a Belgian study of 122 patients with mild chronic hyponatraemia (126 ± 5 mmol/l), falls, gait disturbances and attention deficits were far more common in hyponatraemic patients versus matched controls (58). Also, recent data have shown that elderly patients with bone fractures are over four times as likely to be hyponatraemic as their peers (5). These clinical studies are supported by animal models of hyponatraemia, which show that chronic hyponatraemia induces

severe bone loss in rats (59). Patients with chronic hyponatraemia not only are more prone to falls and fractures, but also are more likely to die when hospitalised for any cause (60); a study conducted in 2006 found that hyponatraemic hospital inpatients had a threefold higher mortality and a 25% longer duration of hospital stay (9). These data have been replicated in a cohort of patients with subarachnoid haemorrhage.

Conclusion

Hyponatraemia is the commonest electrolyte imbalance in hospital inpatients, and it is associated with large and significant morbidity and mortality. SIADH is the most common cause of hyponatraemia in hospital inpatients; correct diagnosis requires accurate assessment of patients' volume status and the outruling of ACTH deficiency and hypothyroidism. The management of SIADH-induced euvolaemic hyponatraemia has traditionally been fluid restriction, but the emerging availability of the vasopressin receptor antagonist class of drugs offers clinicians the opportunity to induce an aquaresis in these patients and physiologically restore their serum sodium level.

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Author contribution statement

All authors contributed to the preparation and submission of the manuscript.

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