

The syndrome of inappropriate antidiuretic hormone: current and future management options

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Abstract

Hyponatraemia is the commonest electrolyte abnormality, and syndrome of inappropriate antidiuretic hormone (SIADH) is the most frequent underlying pathophysiology. Hyponatraemia is associated with significant morbidity and mortality, and as such appropriate treatment is essential. Treatment options for SIADH include fluid restriction, demeclocycline, urea, frusemide and saline infusion, all of which have their limitations. The introduction of the vasopressin-2 receptor antagonists has allowed clinicians to specifically target the underlying pathophysiology of SIADH. Initial studies have shown good efficacy and safety profiles in the treatment of mild to moderate hyponatraemia. However, studies assessing the efficacy and safety of these agents in acute severe symptomatic hyponatraemia are awaited. Furthermore, the cost of these agents at present may limit their use.

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Introduction

The previous article in this supplement established that hyponatraemia due to syndrome of inappropriate antidiuretic hormone (SIADH) is associated with significant morbidity (1), mortality (2–5) and increased length of hospital stay (6). Symptoms are related primarily due to the severity of the hyponatraemia, though the speed of fall in plasma sodium concentration has a major influence on the plasma sodium concentration at which symptoms are noted (7); patients with a rapid fall in plasma sodium are far more likely to experience symptoms than patients with an equivalent level of hyponatraemia which has taken a long time to develop. In addition to symptoms, there is good evidence that patients are subject to serious sequelae of hyponatraemia, including gait abnormalities and falls (8) and increased fracture risk (9). As hyponatraemia is particularly common in the elderly, the latter two morbidities assume greater significance in this age group. With severe hyponatraemia (plasma sodium <120 mmol/l), there is an exponential increase in mortality, with death rates of 50% reported as plasma sodium concentration falls below 115 mmol/l (2).

The symptoms, sequelae and associated mortality therefore dictate that treatment for hyponatraemia due to SIADH is essential to promote patients wellbeing and to lessen the risk of serious complications. Accurate

diagnosis of SIADH and the differentiation from other causes of hyponatraemia is the first essential step in determining appropriate treatment. Diagnostic criteria for SIADH are included in Table 1 (10). In this article, we review the existing treatments available for the management of SIADH and discuss the potential impact of a new class of medications, the vasopressin receptor antagonists or vaptans.

Who needs treatment?

The traditional view is that only severe hyponatraemia (plasma sodium concentrations <125 mmol/l) requires intervention. The neurological sequelae of severe hyponatraemia, which are thought to reflect cerebral oedema, are well recognised, and range from mild headache, nausea and altered cognition to seizures and coma, as the severity of the hyponatraemia worsens, or if the fall in plasma sodium concentration is rapid. Acute falls in plasma sodium concentration can produce life-threatening neurological complications, which may necessitate emergency treatment with hypertonic saline infusion. When a patient has symptoms of hyponatraemia, there is little doubt that active intervention is not simply desirable but essential.

In addition to the threat of neurological complications, hyponatraemia has implications for mortality and length of hospital stay. Gill and colleagues, in a prospective, case-controlled study, found that patients admitted to hospital with severe hyponatraemia (plasma sodium <125 mmol/l) had a higher hospital mortality when compared with normonatraemic admissions (2).

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Table 1 Diagnostic criteria for SIADH (10).

Diagnostic criteria for SIADH
Essential
<ul style="list-style-type: none"> • Plasma osmolality <270 mosmol/kg H₂O • Inappropriate urinary concentration ($U_{osm} > 100$ mosmol/kg H₂O) • Patient is clinically euvolaemic • Elevated urinary sodium (>40 mmol/l), with normal salt and water intake • Exclude hypothyroidism and glucocorticoid deficiency
Supplemental
<ul style="list-style-type: none"> • Abnormal water load test, i.e. inability to excrete at least 90% of a 20 ml/kg water load in 4 h and/or failure to dilute urine to $U_{osm} < 100$ mosmol/kg H₂O • Plasma AVP levels inappropriately elevated relative to plasma osmolality

Tests for supplemental criteria should only be performed in rare situations and in units with expertise in this area as they may aggravate hyponatraemia. Table reproduced with permission from Smith DM, McKenna K & Thompson CJ. Hyponatremia. *Clinical Endocrinology* 2000 **52** 679–678.

Mortality was higher still if hyponatraemia developed during admission, as a result of illness or treatment. Mortality was predictably higher with more severe hyponatraemia. Interestingly, hyponatraemia was associated with greater length of hospital stay, a phenomenon also reported in a separate retrospective study of patients with hyponatraemia due to subarachnoid haemorrhage (6). Neither study was able to determine whether the hyponatraemia was causally associated with longer inpatient stay or simply a marker for more severe disease processes, which warranted prolonged admission *per se*.

Clayton and colleagues also reported greater mortality in patients with hyponatraemia, and in addition found that the excess mortality continued after discharge from hospital, though they were able to conclude that the high mortality reflected the severity of underlying disease processes, in particular congestive cardiac failure and cirrhosis (11). A smaller study from Holland showed important findings (12); when patients with hyponatraemia on admission were compared with those who developed hyponatraemia during hospital stay, there was a similar incidence of neurological symptoms in both the groups, but patients who developed hyponatraemia during admission had a longer duration of admission (31 vs 18 days). Crucially, the authors were able to demonstrate that patients who were not specifically treated for hyponatraemia during hospital admission had higher mortality rates (37 vs 13%). This is the first data to show that inadequate treatment of hyponatraemia leads to worse outcomes. There is also clear data on the improvement in symptoms after treatment of hyponatraemia; in a study of 223 consecutive patients with thiazide-induced hyponatraemia, Chow *et al.* (13) were able to show complete resolution of symptoms (falls, dizziness, lethargy, confusion, headaches and seizures) when hyponatraemia resolved with discontinuation of diuretic therapy.

In contrast to the widespread acceptance that treatment of severe hyponatraemia is important, mild hyponatraemia has been regarded as asymptomatic, and treatment has been considered to be unnecessary. However, it is clear from recent data that mild hyponatraemia is not as benign a condition as previously thought. A recent matched case-control study of 122 patients with hyponatraemia due to SIADH or hypovolaemic hyponatraemia have shown that patients had four times increased likelihood of falls compared with 244 matched controls (adjusted odds ratio 67.4, $P < 0.01$), a difference which was not explainable by an excess of acute illness or medication (8). The frequency of falls was similar in patients with mild hyponatraemia (plasma sodium 130–132 mmol/l, 19%) when compared with severe hyponatraemia (plasma sodium concentration 115–117 mmol/l, 22%). A subgroup of hyponatraemic patients underwent neurocognitive assessment; there were significant abnormalities of gait identified, which improved significantly after correction of hyponatraemia. In a separate study, patients with falls and fractures were more likely to have pre-existing hyponatraemia than patients with falls alone, with even mild hyponatraemia (plasma sodium 131 ± 3 mmol/l) associated with an increased fracture risk in elderly patients (9). Data from rodent studies have shown bone demineralisation in hyponatraemic compared with normonatremic animals, which raise the intriguing possibility that hyponatraemia may predispose to fractures not just by causing gait abnormalities and falls but also by predisposing to osteoporosis (14).

The weight of existing data provides compelling evidence that hyponatraemia is common, confers excess morbidity and mortality and contributes to duration of hospital stay and health economics.

Current treatment options

Fluid restriction

Water restriction is regarded as first-line treatment for hyponatraemia due to SIADH (in the majority of cases apart from patients with severe symptomatic hyponatraemia). It has been established for many years, and in patients in whom there is no question of hypovolaemia, this treatment is safe. Fluid restriction of 800–1200 ml/day is generally advised, according to severity of hyponatraemia. As long as background water losses from the kidney, skin and lungs exceed this amount, there is progressive depletion of total body water and a gradual rise in plasma sodium concentration. The principal drawback is that patients find it extremely difficult to maintain fluid restriction, as thirst in SIADH is inappropriately normal due to a downward resetting of the osmotic thirst threshold (15). Hospitalised inpatients who can be supervised tend to do better with fluid restriction than outpatients, but even inpatients who are receiving fluid with i.v. cytotoxic agents or antibiotics, for instance, find it hard to comply.

As a result, fluid restriction is often insufficient to reverse hyponatraemia, and is rarely quick enough to manage symptomatic hyponatraemia.

Demeclocycline

Demeclocycline is a tetracycline derivative which is utilised in the treatment of SIADH because it causes nephrogenic diabetes insipidus in about 60% of patients for whom it is prescribed. The mode of action is unknown, and the vasopressin resistance is not predictable; in a significant proportion of patients, it does not work. When it does work, the onset of action is also unpredictable, usually occurring after 2–5 days, but occasionally taking longer. In some patients, polyuria can be profound, and patients can become markedly symptomatic, occasionally developing hypernatraemia if access to water is compromised. Nephrotoxicity can arise, particularly in patients with cirrhosis, and although renal impairment is usually reversible with discontinuation, cases with permanent renal failure have been reported (16). It has also been associated with photosensitive skin rash, leading to discontinuation of treatment and return of symptomatic hyponatraemia.

Lithium

Lithium therapy also causes nephrogenic diabetes insipidus in 30% of patients (17), by downregulation of vasopressin-stimulated aquaporin-2 expression (18). An even larger proportion of patients have attenuation of maximal urine concentrating ability (19), and this property of lithium has been utilised by some centres to treat SIADH. The efficacy of lithium is unpredictable as not all patients develop nephrogenic diabetes insipidus, but it is the side effect profile which has caused sufficient concern that most physicians no longer consider it for treatment of SIADH. Nephrogenic diabetes insipidus is usually (20) but not always reversible (21), with chronic treatment sometimes producing interstitial nephritis (22) and end-stage renal failure (23). Additional side effects include hypothyroidism, tremor and rarely, hyperparathyroidism.

Urea

A relatively small number of centres have experience in the use of urea; it is unavailable in many countries, and the unpleasant taste has limited its use. Human studies have shown that long-term (5-year) treatment of hyponatraemia with urea is effective (24), and the same group has published data in a rat model of SIADH which suggests that treatment of hyponatraemia with urea may protect against brain complications such as myelinolysis (25, 26).

Furosemide

Furosemide was shown some years ago to be effective in the rapid correction of hyponatraemia in SIADH (27),

but it is of limited efficacy in long-term treatment as the diuresis that it induces includes a natriuresis, which can occasionally worsen hyponatraemia.

Saline infusion

There is data to suggest that plasma sodium concentration will rise in some patients with SIADH who are treated with i.v. normal (0.9%) saline, particularly if urine osmolality is < 530 mosmol/kg (28). However, treatment with normal saline is generally reserved for patients in whom the differentiation between hypovolaemia and euvolaemia is difficult; in this situation, i.v. saline is a safer first-line treatment than fluid restriction (as fluid restriction may exacerbate hypovolaemic hyponatraemia).

I.v. infusion of hypertonic saline, using either 3 or 5% saline strength, has been described, mainly for the correction of severe hyponatraemia, when patients are at risk of serious or life-threatening neurological sequelae. An expert panel published guidelines for the rate of i.v. infusion of hypertonic saline (29), and the Adrogue–Madias formula has also been used (30). The reason for the perceived need for formulae for infusion rates is the risk of central pontine (or extra pontine) myelinolysis with over-rapid correction of hyponatraemia. There is concern that the Adrogue–Madias equation, for instance, can lead to underestimation of the rate of rise of plasma sodium, and the patient must be carefully monitored with frequent measurement of plasma sodium concentration in order to make sure that the rate of infusion can be adjusted to prevent over-correction (31). A sensible approach is to start off on a fixed low dose infusion rate and adjust the rate of infusion on the basis of 2 hourly plasma sodium concentrations, in order to maintain a rate of rise of plasma sodium concentration of < 0.5 mmol/l per h or 12 mmol over 24 h. The maximum rate of rise of plasma sodium is adjusted down to < 8 mmol/l, in 24 h, in patient groups at greater risk of myelinolysis, such as alcoholics, malnourished individuals and slim young women. It remains to be proven that the vaptans will improve the predictability of the rise in serum sodium in patients with severe symptomatic hyponatraemia compared with patients treated with a well managed hypertonic saline infusion.

Future treatment options: the vaptans

It has been recognised for decades that plasma vasopressin concentrations are elevated in almost every case of SIADH (32). The availability, therefore, of specific antagonists to the vasopressin-2 receptor, the vaptans, has allowed clinicians to specifically target the pathophysiological cause of the disorder. Because the vaptans specifically prevent the reabsorption of water from the renal tubules, without affecting solute excretion, they have been termed aquaretics, to distinguish them from

diuretics, which promote both water and solute excretion. They offer significant potential advantages over existing treatments for SIADH, which are unsatisfactory not just on the basis of lack of efficacy, side effect profile and lack of published evidence, but because they do not target the cause of SIADH.

Vasopressin exerts its antidiuretic effect by binding to the V2 receptors, which are situated in the basolateral surface of the cells of the collecting duct of the kidney. Receptor binding initiates an intracellular cascade which generates adenyl cyclase and an increase of intracellular cAMP. This causes protein synthesis, which leads to the production of mRNA for aquaporin-2, and insertion of pre-formed aquaporin into the apical membrane of the cell, allowing passage of free water across the cell, to be reabsorbed into the renal vasculature (33). The vaptans competitively bind to the V2 receptors, preventing vasopressin-mediated generation of aquaporin-2, thus causing a solute-free aquaresis. A number of V2 receptor antagonists have been studied in the treatment of SIADH, and the papers are documented in Table 2.

The interest in the potential use of vaptans has been heightened by the granting in 2009 of a licence by the European Medicines Agency for the use of tolvaptan specifically for the treatment of adult patients with hyponatraemia secondary to SIADH. Tolvaptan is an oral V2 receptor antagonist which has been shown in healthy individuals to have a greater aquaresis than either frusemide or hydrochlorothiazide, without having a significant natriuresis or kaliuresis (34). The effect of tolvaptan in SIADH was explored in the SALT-1 (conducted in US) and SALT-2 (conducted in US and Europe) trials (35). The patient groups in each study were heterogenous in the causation of hyponatraemia, in that they included individuals with hyponatraemia due to cardiac failure, liver failure and SIADH (~40%). The studies were designed as randomised, placebo-controlled trials of tolvaptan versus placebo; patients were not required to maintain fluid restriction. The tolvaptan dose was adjusted from 15 to 60 mg daily according to clinical need, and was continued for 30 days, with patient monitoring continued for 7 days after discontinuation of tolvaptan.

Mean baseline serum sodium was similar in both the groups at 128 mmol/l, but by day 4 the serum sodium concentration had risen more in the tolvaptan group

than in the placebo group (to 134 vs 130 mmol/l, $P < 0.001$). Serum sodium rose to a mean of 136 mmol/l in the tolvaptan group by the end of the study, but had not changed significantly in the placebo group. The greatest rise in serum sodium concentration was in those patients with the lowest baseline plasma sodium concentration. Side effects were predictable given the action of tolvaptan to increase water excretion, with thirst and dry mouth the most frequent. Serum sodium concentration rose at a greater rate than the maximum recommended rate of 0.5 mmol/l per h in <2% of cases. The results showed that tolvaptan had a predictable effect to increase free water clearance and cause an elevation in serum sodium concentration.

The patients in the SALT studies were not subdivided into separate aetiological subgroups, so that the effects specifically in SIADH patients could not be discerned from the group as a whole (35). In addition, because the mean baseline plasma sodium concentrations (128 mmol/l) reflected a population with moderate hyponatraemia, it is not possible to comment on the effect of tolvaptan in those patients with severe hyponatraemia, in whom significant elevation of plasma sodium concentrations could lead to complication such as myelinolysis. This is particularly an important consideration, given the observation that the greatest rise in plasma sodium occurred in those patients with the lowest baseline concentrations. Further work is necessary to determine whether the rate of rise of plasma sodium concentration in patients with severe hyponatraemia is sufficiently predictable and controllable to allow tolvaptan to replace hypertonic saline in this situation. However, the data would indicate that tolvaptan has an acceptable safety profile, and is predictable in the treatment of mild to moderate hyponatraemia due to SIADH. Data from the SF-12 Mental Component Score readings in the study showed that the mean score improved in the tolvaptan group from readings comparable to those derived from patients with depression, close to the normal adult mean at the end of treatment, indicating that the rise in plasma sodium concentration observed during the study was symptomatically beneficial.

Verbalis (36) published data from a subgroup analysis of patients with euvoelaemic hyponatraemia treated with either i.v. conivaptan or placebo. Although patients who needed emergency treatment with hypertonic saline were excluded from the study, patients with plasma sodium concentrations as low as 115 mmol/l were included in the protocol. The results of this study were similar to those for tolvaptan, with conivaptan causing significant elevations in plasma sodium concentration compared with placebo, with little in the way of serious adverse events; infusion reactions were the commonest side effect. This study, conducted in a population of predominantly SIADH patients, confirmed the important role that the vaptans are likely to play in the treatment of this condition.

Table 2 V2 receptor antagonists in the treatment of SIADH.

Drug	Receptor action	Mode of administration	References
Tolvaptan	V2	Oral	(35, 40)
Conivaptan	V1a and V2	I.v./oral	(24, 36, 37, 41, 42)
Lixivaptan	V2	Oral	(43)
Mozavaptan	V2	Oral	(44)
Satavaptan	V2	Oral	(45)

V1 and V2, vasopressin receptors 1 and 2.

The most likely role for vaptans in the immediate future is in the treatment of mild to moderate hyponatraemia due to SIADH. Because there is a paucity of data in symptomatic severe hyponatraemia, hypertonic saline is likely to remain the treatment of choice in this group until more data are available to the clinician. Although mild hyponatraemia has traditionally been treated with water restriction as first-line therapy, the difficulty with patient compliance in SIADH, due to the downward resetting of the thirst threshold (15), means that the vaptans are likely to replace water restriction as first-line treatment. The fact that both tolvaptan (35) and conivaptan (currently only licensed in the USA) (37) are effective without the need for fluid restriction means that patient acceptability will be superior to that of water restriction. The extent to which vaptans replace fluid restriction as first-line therapy may be predicated upon appropriate pricing of the drug to allow it to be accommodated in hard pressed therapeutic budgets. An important determinant of competitive pricing may be the potential for treatment of hyponatraemia to negate the extra financial burden associated with the condition. A number of studies have documented increased duration of hospital stay (6, 38) and intensive care stay (4, 38), in patients with hyponatraemia due to disparate causes. One of these studies calculated that hyponatraemia in pneumonia patients was associated with an excess of \$1300 to total hospital costs (this was a study based in the USA and cost implications in other medical systems may be different) (38). Analysis of data from the Integrated Health Care Information Services National Managed Care Benchmark Database in the United States calculated that hyponatraemia was a predictor on cumulative medical costs at 6 months (41% increase) and 12 months (46%) after discharge from hospital (39). At present, the data are not available; however, if it can be shown that treatment of SIADH can ameliorate some of the financial burden associated with hyponatraemia, the current relatively high unit costs of the vaptans may make fiscal sense to health care providers.

Tolvaptan has specifically been licenced in Europe for the treatment of euvolaemic hyponatraemia, and it is specifically, and correctly, not recommended for hypovolaemic hyponatraemia. Because the aquaresis generated by tolvaptan will further reduce extracellular fluid volume, treatment of hypovolaemic hyponatraemia with this drug would worsen the clinical situation. Although it is not always easy to differentiate between euvolaemia and mild hypovolaemia, this is a challenge which must be considered by the prescribing physician; in cases of diagnostic doubt, a careful 0.9% saline challenge may be the safest first step. Patients with hypovolaemic hyponatraemia are likely to respond well to i.v. 0.9% saline, with a significant rise in plasma sodium and a fall in blood urea; patients with SIADH are likely to have a modest response, if any.

SIADH complicates ~30% of patients with subarachnoid haemorrhage (6). Data on the response of SIADH due to subarachnoid haemorrhage to treatment with vaptans have not been published to date. Neurosurgeons are keen to avoid hypovolaemia and the potential for cerebral vasospasm, so treatment of this group of patients should probably wait for careful, controlled studies.

Conclusions

Hyponatraemia is the commonest electrolyte abnormality, and SIADH is the most frequent underlying pathophysiology. Hyponatraemia is associated with significant morbidity and mortality, and as such appropriate treatment is essential. Treatment options for SIADH include fluid restriction, demeclocycline, urea, frusemide and saline infusion, all of which have their limitations. The introduction of the vasopressin-2 receptor antagonists has allowed clinicians to specifically target the underlying pathophysiology of SIADH. Initial studies have shown good efficacy and safety profiles in the treatment of mild to moderate hyponatraemia. However, studies assessing the efficacy and safety of these agents in acute severe symptomatic hyponatraemia are awaited. Furthermore, the cost of these agents at present may limit their use.

Declaration of interest

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