Hyponatraemia – Current Treatment Strategies and Perspectives for the Future

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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 management of hyponatraemia is predicated on correct diagnosis of the underlying cause, which relies on accurate assessment of the patient’s volume status. The syndrome of inappropriate antidiuresis (SIAD) is the most common cause of hyponatraemia and current treatments for this syndrome are poorly effective. Hypervolaemic hyponatraemia is also difficult to manage. The emergence of a new class of medications – the selective vasopressin-2 receptor antagonists or vaptans – gives clinicians an opportunity to target the underlying pathophysiology of these conditions, and represents an exciting new development in the management of hyponatraemia. In this article we review the differential diagnosis of hyponatraemia, current treatment strategies and emerging management options.

Keywords

Hyponatraemia, mortality, differential diagnosis, syndrome of inappropriate antidiuresis (SIAD), vaptans

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Hyponatraemia is by far the most common electrolyte imbalance found in hospital inpatients,¹ and patients with symptomatic hyponatraemia have a vastly increased mortality compared with normonatraemic controls.² Therefore, it is essential that hyponatraemic patients receive effective and targeted therapy. However, hyponatraemia has many 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 recent emergence of the vaptan class of aquaretic agents is an exciting new development in the management of euvolaemic hyponatraemia, but hyponatraemia remains poorly managed. In this article, we review the diagnosis of hyponatraemia, current management strategies and emerging therapeutic options.

Prevalence and Effects of Hyponatraemia

Hyponatraemia is by far the most common electrolyte abnormality in hospital inpatients, and is also common in healthy patients in the community. The prevalence of mild hyponatraemia (<135 mmol/l) was quoted as 4 % in a recent Belgian study,³ which looked at a healthy, elderly population. The incidence of new hyponatraemia in hospitalised patients is far higher – a recent study showed that 8 % of patients admitted with pneumonia developed hyponatraemia during the course of hospital admission;¹ and our own data shows that 56 % of patients admitted with subarachnoid haemorrhage develop hyponatraemia.¹ Other neurosurgical patients also have high rates of hyponatraemia, with between 10 and 20 % of patients with intracranial tumours, haematomas undergoing pituitary surgery developing hyponatraemia.⁴ These high prevalence rates are important due to almost universal findings of higher morbidity and 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 %, significantly higher than in eunatraemic controls (9 %).⁵ Mortality in this study increased exponentially as plasma sodium fell. This excess mortality has also been shown to persist for months after discharge from hospital,⁶ although at least some of this excess mortality was attributed to the illnesses which precipitated hyponatraemia, such as cardiac failure, liver disease, and small cell carcinoma of the lung. However, hyponatraemia itself has recently been shown to be implicated in the mortality suffered by these patients, with higher mortality rates in hyponatraemic patients who did not receive specific treatment for hyponatraemia compared with those who did (37 versus 13 %).⁷ It has also been shown that of commonly measured clinical and biochemical parameters in acute hospital admissions, plasma sodium concentration was most strongly associated with in-hospital mortality, with an odds ratio of 4.4.⁸ Hyponatraemia has also been associated with increased duration of hospital stay with resultant increased hospital costs.⁹ The adverse outcomes outlined above that are associated with hyponatraemia are not confined to patients with plasma sodium <125 mmol/l. Patients with mild hyponatraemia in the community,³ with pneumonia,⁴ and in intensive care¹¹ have all been shown to have excess mortality compared with patients with normal plasma sodium concentrations. The largest study to date on this topic showed that even mild hyponatraemia in hospital inpatients (which occurred in
14.5 % of those studied) increased mortality at one year and five years. A recent analysis of the American National Health and Nutrition Examination Survey III (NHANES III) database has revealed that mild (mean 133 mmol/l) chronic hyponatraemia is associated with osteoporosis at the femoral neck. These recent data have challenged the traditional view of mild hyponatraemia as an asymptomatic condition and renewed interest in the treatment of hyponatraemia of all levels of severity.

**Differential Diagnosis of Hyponatraemia**

The first step in the treatment of hyponatraemia is correct diagnosis of the underlying aetiology. There are a number of classifications of the pathogenesis of hyponatraemia. Some authorities use a classification based on whether hyponatraemia is dilutional, depletional, or redistributinal in nature. In routine clinical practice, we classify hyponatraemia based on clinical and biochemical estimation of extracellular volume status. This divides hyponatraemia into hypovolaemic, euvoalaemic, and hypervolaemic aetiologies (see Table 1). Although the clinical features of the three categories are quite distinct, in practice it can be difficult to distinguish mild hyponatraemia from euvoalaemia. The causes of hyponatraemia are numerous and 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 SIAD due to anorexia. In these cases, an isotonic saline infusion can be helpful.

Euvolaemic hyponatraemia, usually caused by the syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatraemia in hospitalised patients. However, it is important that SIAD is not diagnosed erroneously as a number of other pathologies can result in euvoalaemic hyponatraemia, for which the management is markedly different. For example, hyponatraemia may occur as a direct result of surgical procedures – bladder irrigation during transurethral resection of the prostate gland can lead to direct absorption of water from the bladder, producing euvoalaemic dilutional hyponatraemia, and inappropriate fluid replacement may also cause dilutional hyponatraemia. Adrenocorticotropic hormone (ACTH) deficiency, which leads to cortisol but not aldosterone deficiency, can cause euvolaemic hyponatraemia with a biochemical picture identical to SIAD. This is due to the fact that plasma cortisol is necessary to excrete free water. This distinction is especially important to make in patients with neurosurgical conditions, who commonly develop hyponatraemia. Over 50 % of patients with acute subarachnoid haemorrhage develop hyponatraemia, most of which has been attributed to SIAD. Some of the hyponatraemia attributed in the immediate post-haemorrhage period to SIAD may actually represent acute ACTH deficiency. This is as yet unproven; however, 16 % of patients with acute traumatic brain injury develop ACTH deficiency and some of these patients develop very severe hyponatraemia.

**Current Treatment of Hyponatraemia**

As outlined above, the management of hyponatraemia is critically dependent on an accurate estimation of the patient’s extracellular volume status, and the accurate diagnosis of the underlying cause (see Table 1). Incorrect diagnosis of the patient’s volume status could lead to harmful or even fatal mistakes in treatment.

In hypovolaemic hyponatraemia, the aim is to correct plasma sodium and simultaneously restore intravascular volume. Most cases will respond to the intravenous infusion of 0.9 % isotonic saline. Diuretic therapy should be discontinued, and an underlying cause sought and treated. Co-existent Addison’s disease is suggested by history, examination, and the presence of hyperkalaemia. Although the biochemical abnormalities of Addison’s disease will respond to high-dose corticosteroids, patients usually need intravenous saline to expand blood volume and replace body sodium; intravenous dextrose may also be needed if the patient is hypoglycaemic.

Euvolaemic hyponatraemia is usually, but not always, due to syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), and therefore the most important element in diagnosis is the recognition of other causes, especially glucocorticoid deficiency. Glucocorticoid therapy has been shown to suppress arginine vasopressin (AVP) secretion, which allows free water excretion and the normalisation of plasma sodium concentrations in patients with ACTH deficiency.

Fluid restriction is regarded as the first-line treatment for hyponatraemia due to SIAD (in the majority of cases apart from patients with severe symptomatic hyponatraemia). It is well established and safe. Fluid restriction of 800–1,200 ml per day is generally advised, according to severity of hyponatraemia. Over 80 % of patients for whom it is prescribed, diabetes insipidus in about 60 % of patients for whom it is prescribed, and so is sometimes used to treat SIAD. Its mode of action is unknown and unpredictable; it is often ineffective. The onset of action is also unpredictable, usually occurring after two to five days, but occasionally taking longer. Conversely, some patients may develop

**Table 1: Differential Diagnosis of Hyponatraemia**

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Urinary Na⁺ &lt;20 mmol/l</th>
<th>Urinary Na⁺ &gt;40 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemic</td>
<td>Dry mucous membranes</td>
<td>Gastrointestinal losses</td>
</tr>
<tr>
<td></td>
<td>Decreased turgor</td>
<td>Mucosal losses</td>
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<td></td>
<td>Tachycardia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Hypotension (orthostatic)</td>
<td>Sodium depletion</td>
</tr>
<tr>
<td></td>
<td>Raised urea, renin</td>
<td>post diuretics</td>
</tr>
<tr>
<td>Euvolaemic</td>
<td>Underlying illness</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SIAD with ongoing fluid restriction</td>
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<tr>
<td></td>
<td></td>
<td>Primary polydipsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate fluid replacement</td>
</tr>
<tr>
<td>Hypervolaemic</td>
<td>Peripheral, pulmonary oedema</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Underlying illness</td>
<td>Nephrotic syndrome</td>
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ACTH = adrenocorticotrophic hormone; AVP = jugular venous pulse; Na⁺ = sodium; SIAD = syndrome of inappropriate antidiuresis.
profound polyuria and even hyponatraemia. Reversible and even permanent nephrotoxicity can arise, particularly in patients with cirrhosis. It may also cause photosensitive skin rash. Lithium therapy also causes nephrogenic diabetes insipidus in 30% of patients, by downregulation of vasopressin-stimulated aquaporin-2 expression, but similar to demeclocycline its efficacy is unpredictable as not all patients develop nephrogenic diabetes insipidus, and it also has multiple side effects. These include permanent nephrogenic diabetes insipidus, interstitial nephritis, end-stage kidney disease, hypothyroidism and hyperparathyroidism.

There is no consensus in terms of how fast hyponatraemia should be corrected in acute severe hyponatraemia. The risk for CPM is less in acute hyponatraemia, and treatment needs to be rapid to avoid cerebral oedema and death. However, CPM is still a major concern if correction is over-rapid. An expert panel published guidelines for the rate of intravenous infusion of hypertonic saline and the Adrogue – Madias formula has also been used. However, the Adrogue – Madias equation 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 prevent over-correction. Our unit would start therapy with a fixed low-dose infusion rate and adjust the rate of infusion on the basis of two-hourly plasma sodium concentrations, in order to maintain a rate of rise of plasma sodium concentration of 0.5 mmol/l/hour, or 12 mmol/l over 24 hours. The maximum rate of rise of plasma sodium should be <8 mmol/l/24 hours in patient groups at greater risk for CPM, such as alcoholics, malnourished individuals, and slim young women.

Urea is used in some centres in the management of SIAD; however, it is unavailable in many countries and the unpleasant taste has limited its use. Long-term treatment of hyponatraemia with urea is effective and the does not appear to lead to the development of severe complications such as myelinolysis. Frusemide may also be effective in the rapid correction of hyponatraemia in SIAD, but as it is a natriuretic agent, it may actually worsen hyponatraemia.

It is often difficult to clinically differentiate between hypovolaemia and euvoalaemia. In these patients, intravenous saline is a safer first-line treatment than fluid restriction (as fluid restriction may exacerbate hypovolaemic hyponatraemia). Plasma sodium concentration will rise in some patients with SIAD who are treated with isotonic saline, particularly if urine osmolality is >550 mOsm/kg. However, this is only effective in a minority of patients.

In hypervolemic hyponatraemia, therapy is again aimed at the underlying cause. In congestive cardiac failure and cirrhosis, the mainstays of therapy are a combination of diuretics and fluid restriction to normalize total body water, in combination with inhibition of the renin angiotensin axis using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or spironolactone. Much research has focused on the development of aquaretic agents to correct total body water and hence correct serum sodium in both euvoalaemic and hypervolemic hyponatraemia; these will be discussed in more detail below.

The two pivotal trials of tolvaptan were Study of ascending plasma sodium concentration in order to prevent over-correction. The maximum rate of rise of plasma sodium should be <8 mmol/l/24 hours in patient groups at greater risk for CPM, such as alcoholics, malnourished individuals, and slim young women. The maximum rate of rise of plasma sodium concentration is long standing. The risk is much higher in patients with chronic alcohol abuse, and in young women. The main figure that is not to be exceeded in chronic hyponatraemia is a sodium correction rate of 0.5 mmol/l/hour. If plasma sodium is corrected more rapidly than this, there is a rapid restoration of intracellular sodium and potassium, but extracellular organic solutes may take five to seven days to normalise. This leads to a hypertonic extracellular compartment that causes extracellular movement of water to the myelin sheath outside the nerve cell. This leads to intramyelinic oedema, osmotic endothelial injury, and local release of myelinotoxic factors, precipitating oligodendrocyte failure and death.

In hypervolemic hyponatraemia due to cardiac failure and cirrhosis, treatment than fluid restriction (as fluid restriction may exacerbate hypovolaemic hyponatraemia). Plasma sodium concentration will rise in some patients with SIAD who are treated with isotonic saline, particularly if urine osmolality is >550 mOsm/kg. However, this is only effective in a minority of patients.

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Treatment of severe hyponatraemia is of particular importance as untreated severe hyponatraemia, especially when associated with evidence of cerebral irritation such as seizures, is potentially fatal and recovery may occur with permanent brain damage. However, treatment is also hazardous with the risk for developing cerebral demyelination, characterised by spastic quadriparesis, cranial nerve palsies, pseudobulbar palsy, with behavioural changes, altered cognition and pseudodementia, with consequent water retention and dilutional hyponatraemia. Specific antagonists to the vasopressin–2 receptor have now been developed. This new class of drugs is termed the vaptan class and is the first treatment for SIAD and hypervolemic hyponatraemia, which targets the underlying physiology. The vaptans can be described as aquaretic rather than diuretic agents as they specifically prevent the reabsorption of water from the renal tubules.

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. The binding of vasopressin to its receptor initiates an intracellular cascade resulting in an increase of intracellular cyclic adenosine monophosphate (cAMP). This causes protein synthesis, which leads to the production of messenger RNA (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. This free water is then reabsorbed into the renal vasculature and from there to the systemic circulation. The vaptans competitively bind to the V2 receptors, preventing the generation of aquaporin-2, thus causing a solute-free aquareasis.

The use of the vaptans as a treatment for SIAD began in 2009 when the European Medicines Agency (EMA) granted a licence for the use of tolvaptan specifically for the treatment of adult patients with hyponatraemia secondary to SIAD. In the US, this medication has also been licensed for the treatment of hypervolemic hyponatraemia. Tolvaptan is an oral V2 receptor antagonist that has been shown in healthy individuals to have a greater aquareasis than either frusemide or hydrochlorothiazide, without having a significant natriuresis or kaliuresis. The two pivotal trials of tolvaptan were Study of ascending plasma sodium concentration in order to prevent over-correction. The maximum rate of rise of plasma sodium concentration should be <8 mmol/l/24 hours in patient groups at greater risk for CPM, such as alcoholics, malnourished individuals, and slim young women.

**Future Treatment Strategies for Hyponatraemia**

As outlined above, SIAD is one of the most common causes of hyponatraemia; it is also the cause for which current available treatments are unsatisfactory. Current treatments for hypervolemic hyponatraemia are also poor, with the development of hyponatraemia being recognised as a poor prognostic indicator in cardiac failure and cirrhosis. It has been recognised for decades that plasma vasopressin concentrations are elevated in almost every case of SIAD. It is also known that the fall in mean arterial pressure in hypervolemic hyponatraemia due to cardiac failure and cirrhosis stimulates baroregulated vasopressin secretion, baroregulated activation of the rennin-angiotensin-aldosterone axis, and increased sympathetic tone, with consequent water retention and dilutional hyponatraemia. Specific antagonists to the vasopressin–2 receptor have now been developed. This new class of drugs is termed the vaptan class and is the first treatment for SIAD and hypervolemic hyponatraemia, which targets the underlying physiology. The vaptans can be described as aquaretic rather than diuretic agents as they specifically prevent the reabsorption of water from the renal tubules.
levels of tolvaptan in hyponatraemia 1 (SALT-1) (conducted in the US) and SALT-2 (conducted in the US and Europe) trials.2 These studies included individuals with hyponatraemia due to cardiac failure, liver failure, and SIAD. Both 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 15–60 mg daily according to clinical need, and continued for 30 days, with patient monitoring continued for seven days after discontinuation of tolvaptan. Mean baseline serum sodium was similar in both groups at 128 mmol/l. Serum sodium underwent a predictable rise to a mean of 136 mmol/l in the tolvaptan group by the end of the study and did not change significantly in the placebo group. The greatest rise in serum sodium concentration was in those patients with the lowest baseline plasma sodium concentration.

The most likely role for the vaptans in the immediate future is in the normalisation of plasma sodium concentrations. However, patients on conivaptan therapy led to a safe, effective, and predictable and controllable rise in plasma sodium concentration in those patients who have severe, acute, symptomatic hyponatraemia and who are currently managed with hypertonic saline. The best data looking at a more severely hyponatraemic cohort is taken from a study on the management of hyponatraemia with either intravenous conivaptan (a compound not yet available in Europe) or placebo.35 Subgroup analysis of those subjects with SIAD, some of whom had plasma sodium concentrations as low as 115 mmol/l, showed that conivaptan therapy led to a safe, effective, and predictable normalisation of plasma sodium concentrations. However, patients requiring emergency treatment with hypertonic saline were excluded.

The most likely role for the vaptans in the immediate future is in the treatment of mild to moderate hyponatraemia due to SIAD. None are yet licensed for the management of hypervolemic hyponatraemia in Europe, and they are not yet proven in the management of acute, symptomatic, severe hyponatraemia. The vaptans may replace water restriction as first-line treatment for SIAD, given the frequent failure of fluid restriction and the fact that tolvaptan is effective without the need for fluid restriction.30 However, the high cost of the vaptans compared with fluid restriction may limit their usage. This potential stumbling block may be overcome by the fact that a number of recent studies have shown that hyponatraemia increases duration of hospital stay41 and intensive care stay,41 regardless of the cause.

Data from the Integrated Health Care Information Services National Managed Care Benchmark Database in the US calculated that hyponatraemia was a predictor on cumulative medical costs at six months (41 % increase) and 12 months (46 %) after discharge from hospital.46 Therefore, there is a growing acceptance that hyponatraemia significantly increases healthcare costs; if future studies can show that vaptan therapy reduces this cost by safely and effectively correcting hyponatraemia then their current high costs may become more acceptable.

The other potential problem with widespread use of the vaptans is that of inappropriate prescription; specifically their incorrect use in hypovolemic hyponatraemia that would worsen the clinical situation. It is not always easy to differentiate between euvoelaemia and mild hypovolaemia, if the diagnosis is uncertain a careful isotonic saline challenge may be the safest first step. Patients with hypovolemic hyponatraemia are likely to respond well whereas patients with SIAD are likely to have a modest response, if any. Thus, despite the availability of an exciting new class of therapeutic agents, clinical acumen remains essential to the accurate diagnosis and management of hyponatraemia.51

Conclusion

Hyponatraemia is the most commonly encountered electrolyte abnormality and is associated with significant morbidity and mortality. Effective treatment is therefore necessary for all levels of hyponatraemia. Correct evaluation of the patient’s volume status is essential to accurately diagnose the underlying cause of hyponatraemia. SIAD is the most common pathophysiological process underlying hyponatraemia and current treatment modalities for this syndrome are poorly effective.

The development of the vaspesspin-2 receptor antagonist class of medications gives clinicians the ability to target the underlying pathophysiology of SIAD and hypervolemic hyponatraemia. However, use of these agents may be restricted by their cost. Furthermore, more data is required in terms of the use of these agents in acute severe symptomatic hyponatraemia.

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