

Hyponatremia—Current Treatment Strategies and Perspectives for the Future

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Abstract

Hyponatremia is the commonest electrolyte abnormality found in hospital inpatients and is associated with a greatly increased morbidity and mortality. The management of hyponatremia 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 hyponatremia and current treatments for this syndrome are poorly effective. Hypervolemic hyponatremia 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 represent an exciting new development in the management of hyponatremia. In this article we review the differential diagnosis of hyponatremia, current treatment strategies, and emerging management options.

Keywords

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

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Hyponatremia is by far the most common electrolyte imbalance found in hospital inpatients,¹ and patients with symptomatic hyponatremia have a vastly increased mortality compared with normonatremic controls.² Therefore, it is essential that hyponatremic patients receive effective and targeted therapy. However, hyponatremia 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 euvoletic hyponatremia, but hyponatremia remains poorly managed. In this article, we review the diagnosis of hyponatremia, current management strategies, and emerging therapeutic options.

Prevalence and Effects of Hyponatremia

Hyponatremia 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 hyponatremia (<135 mmol/l) was quoted as 4 % in a recent Belgian study,³ which looked at a healthy, elderly population. The incidence of new hyponatremia in hospitalized patients is far higher—a recent study showed that 8 % of patients admitted with pneumonia developed hyponatremia during the course of hospital admission,⁴ and our own data shows that 56 % of patients admitted with subarachnoid hemorrhage develop hyponatremia.⁵ Other neurosurgical patients also have high rates of hyponatremia, with between 10–20 % of patients with intracranial tumours, hematomas undergoing pituitary surgery developing hyponatremia.⁶

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 hospitalized patients with plasma sodium concentration <125 mmol/l showed an overall mortality of 28 %, significantly higher than in eunatremic controls (9 %).⁷ 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,⁸ although at least some of this excess mortality was attributed to the illnesses which precipitated hyponatremia, such as cardiac failure, liver disease, and small cell carcinoma of the lung. However, hyponatremia itself has recently been shown to be implicated in the mortality suffered by these patients, with higher mortality rates in hyponatremic patients who did not receive specific treatment for hyponatremia compared with those who did (37 versus 13 %).⁹ 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 4.4.¹⁰ Hyponatremia has also been associated with increased duration of hospital stay with resultant increased hospital costs.^{5,7}

The adverse outcomes outlined above associated with hyponatremia are not confined to patients with plasma sodium <125 mmol/l. Patients with mild hyponatremia 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 hyponatremia in

hospital inpatients (which occurred in 14.5 % of those studied) increased mortality at one year and five years.¹² 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 hyponatremia is associated with osteoporosis at the femoral neck.¹³ These recent data have challenged the traditional view of mild hyponatremia as an asymptomatic condition and renewed interest in the treatment of hyponatremia of all levels of severity.

Differential Diagnosis of Hyponatremia

The first step in the treatment of hyponatremia is correct diagnosis of the underlying etiology. There are a number of classifications of the pathogenesis of hyponatremia. Some authorities use a classification based on whether hyponatremia is dilutional, depletional, or redistributional in nature.¹⁴ In routine clinical practice, we classify hyponatremia based on clinical and biochemical estimation of extracellular volume status. This divides hyponatremia into hypovolemic, euvoletic, and hypervolemic etiologies (see *Table 1*). Although the clinical features of the three categories are quite distinct, in practice it can be difficult to distinguish mild hypovolemia from euvolemia. The causes of hyponatremia are numerous and diverse, and so accurate diagnosis is essential to enable correct management. Hypovolemic hyponatremia can be difficult to diagnose as serum urea may be low in hypovolemic elderly patients and urinary sodium may be low in SIAD due to anorexia. In these cases, an isotonic saline infusion can be helpful.¹⁵

Euvoletic hyponatremia, usually caused by the syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatremia in hospitalized patients. However, it is important that SIAD is not diagnosed erroneously as a number of other pathologies can result in euvoletic hyponatremia, for which the management is markedly different. For example, hyponatremia 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 euvoletic dilutional hyponatremia,^{16,17} and inappropriate fluid replacement may also cause dilutional hyponatremia.¹⁸ Adrenocorticotrophic hormone (ACTH) deficiency, which leads to cortisol but not aldosterone deficiency, can cause euvoletic hyponatremia with a biochemical picture identical to SIAD. This is due to the fact that plasma cortisol is necessary to excrete free water.¹⁹ This distinction is especially important to make in patients with neurosurgical conditions, who commonly develop hyponatremia.⁶ Over 50 % of patients with acute subarachnoid hemorrhage develop hyponatremia, most of which has been attributed to SIAD.⁷ Some of the hyponatremia attributed in the immediate post-hemorrhage 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 deficiency²⁰ and some of these patients develop very severe hyponatremia.²¹

Current Treatment of Hyponatremia

As outlined above, the management of hyponatremia 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.

Table 1: Differential Diagnosis of Hyponatremia

	Clinical Signs	Urinary Na+ <20 mmol/l	Urinary Na+ >40 mmol/l
Hypovolemic	Dry mucous membranes Decreased turgor Tachycardia Hypotension (orthostatic) Raised urea, renin	Gastrointestinal losses Mucosal losses Pancreatitis Sodium depletion post diuretics	Diuretics Addison's disease Cerebral salt wasting Salt-wasting nephropathy
Euvoletic	Underlying illness	Hypothyroidism SIAD with ongoing fluid restriction Primary polydipsia Inappropriate fluid replacement	SIAD ACTH deficiency
Hypervolemic	Peripheral, pulmonary edema Ascites Raised JVP Underlying illness	Cirrhosis Cardiac failure Nephrotic syndrome	Cardiac failure or cirrhosis on diuretic therapy

ACTH = adrenocorticotrophic hormone; JVP = jugular venous pulse; Na = sodium; SIAD = syndrome of inappropriate antidiuresis.

In hypovolemic hyponatremia, 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 hyperkalemia. 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 hypoglycemic.

Euvoletic hyponatremia 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,²² which allows free water excretion and the normalisation of plasma sodium concentrations in patients with ACTH deficiency.²³

Fluid restriction is regarded as the first-line treatment for hyponatremia due to SIAD (in the majority of cases apart from patients with severe symptomatic hyponatremia). It is well established and safe. Fluid restriction of 800–1,200 ml per day is generally advised, according to severity of hyponatremia. However, strict fluid restriction is extremely difficult to maintain, especially in the community, as thirst in SIAD is inappropriately normal due to a downward resetting of the osmotic thirst threshold.²⁴ Furthermore, intravenous antibiotic or cytotoxic therapy alone can push patients over their allotted fluid restriction. As a result, fluid restriction is often insufficient to reverse hyponatremia and is rarely quick enough to manage symptomatic hyponatremia.

Hyponatremia

Demeclocycline is a tetracycline derivative that causes nephrogenic 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 profound polyuria and even hypernatremia. Reversible and even permanent nephrotoxicity can arise, particularly in patients with cirrhosis.²⁵ It may also cause photosensitive skin rash. Lithium therapy also causes nephrogenic diabetes insipidus in 30 % of patients,²⁶ by downregulation of vasopressin-stimulated aquaporin-2 expression,²⁷ 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,²⁸ interstitial nephritis,²⁹ end-stage kidney disease,³⁰ hypothyroidism, and hyperparathyroidism.

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 hyponatremia with urea is effective³¹ and does not appear to lead to the development of severe complications such as myelinolysis.^{32,33} Frusemide may also be effective in the rapid correction of hyponatremia in SIADH,³⁴ but as it is a natriuretic agent, it may actually worsen hyponatremia.

It is often difficult to clinically differentiate between hypovolemia and euvolemia. In these patients, intravenous saline is a safer first-line treatment than fluid restriction (as fluid restriction may exacerbate hypovolemic hyponatremia). Plasma sodium concentration will rise in some patients with SIADH who are treated with isotonic saline, particularly if urine osmolality is <530 mOsm/kg.²⁸ However, this is only effective in a minority of patients.

In hypervolemic hyponatremia, 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 euvolemic and hypervolemic hyponatremia; these will be discussed in more detail below.

Treatment of severe hyponatremia is of particular importance as untreated severe hyponatremia, 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, characterized by spastic quadriparesis, cranial nerve palsies, pseudobulbar palsy, with behavioural changes, altered cognition, and 'locked in syndrome'. This usually affects the pontine area (known as central pontine myelinolysis [CPM]), but 10 % of cases involve the cerebellum, thalamus, midbrain, and lateral geniculate body³⁵ and is caused by over-rapid correction of hyponatremia, usually when the low 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 hyponatremia is a sodium correction rate of 0.5 mmol/l/hour.³⁶ 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 normalize. 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 edema, osmotic endothelial injury, and local release of myelinotoxic factors, precipitating oligodendrocyte failure and death.³⁷

There is no consensus in terms of how fast hyponatremia should be corrected in acute severe hyponatremia. The risk for CPM is less in acute hyponatremia, and treatment needs to be rapid to avoid cerebral edema 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 saline³⁸ and the Adrogue—Madias formula has also been used.³⁹ 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.⁴⁰ 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.

Future Treatment Strategies for Hyponatremia

As outlined above, SIAD is one of the most common causes of hyponatremia; it is also the cause for which current available treatments are unsatisfactory. Current treatments for hypervolemic hyponatremia are also poor, with the development of hyponatremia being recognized as a poor prognostic indicator in cardiac failure⁴¹ and cirrhosis.⁴² It has been recognized for decades that plasma vasopressin concentrations are elevated in almost every case of SIAD.⁴³ It is also known that the fall in mean arterial pressure in hypervolemic hyponatremia due to cardiac failure and cirrhosis stimulates baroregulated vasopressin secretion, baroregulated activation of the renin-angiotensin-aldosterone axis, and increased sympathetic tone,⁴⁴ with consequent water retention and dilutional hyponatremia. 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 hyponatremia, 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 vasculature⁴⁵ 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 aquaresis.

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 hyponatremia secondary to SIAD. In the US, this medication has also been licensed for the treatment of hypervolemic hyponatremia. Tolvaptan is an oral V2 receptor antagonist that has been shown in healthy individuals to have a greater aquaresis than either frusemide or hydrochlorothiazide, without having a significant natriuresis or kaliuresis.⁴⁶ The two pivotal trials of tolvaptan were Study of ascending levels of tolvaptan in hyponatremia 1 (SALT-1) (conducted in US) and SALT-2 (conducted in US and Europe) trials.⁴⁷ These studies included individuals with hyponatremia due to cardiac failure, liver failure, and SIAD. Both studies were designed as randomized, 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 main side effects encountered were thirst and dry mouth due to the aquaretic effect of tolvaptan. A small number of patients had a serum sodium concentration rise of more than 0.5 mmol/L/hour; none suffered any neurological sequela. An open-label extension of the SALT-1 and -2 studies of almost two years duration showed that the serum sodium normalisation was sustained and only five of 111 patients experienced an over-rapid correction of serum sodium levels, with one of 111 developing hypernatremia.⁴⁸ None of these patients developed any neurological complications. The SALT studies also examined the Short Form 12 (SF-12) Mental Component Scores before and after therapy; the mean scores significantly improved in the hyponatremic cohort, indicating that treatment was symptomatically beneficial.

The mean baseline plasma sodium concentration in SALT-1 and -2 was 128 mmol/L, thus it is not possible to comment on the effect of tolvaptan in those patients with severe hyponatremia who are at most risk for CPM. This is a particularly important consideration, given the observation that the greatest rise in plasma sodium occurred in those patients with the lowest baseline concentrations. Therefore, there is not yet enough evidence to show that tolvaptan can induce a predictable and controllable rise in plasma sodium concentration in those patients who have severe, acute, symptomatic hyponatremia and who are currently managed with hypertonic saline. The best data looking at a more severely hyponatremic cohort is taken from a study on the management of hyponatremia with either intravenous conivaptan (a compound not yet available in Europe) or placebo.⁴⁹ 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 hyponatremia due to SIAD. None are yet licensed for the management of hypervolemic hyponatremia in Europe, and they are not yet proven in the management of acute, symptomatic, severe hyponatremia. 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.⁴⁷ 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 hyponatremia increases duration of hospital stay^{4,5} and intensive care stay,^{4,11} regardless of the cause.

Data from the Integrated Health Care Information Services National Managed Care Benchmark Database in the US calculated that hyponatremia was a predictor on cumulative medical costs at six months (41 % increase) and 12 months (46 %) after discharge from hospital.⁵⁰ Therefore, there is a growing acceptance that hyponatremia significantly increases healthcare costs; if future studies can show that vaptan therapy reduces this cost by safely and effectively correcting hyponatremia 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 hyponatremia that would worsen the clinical situation. It is not always easy to differentiate between euvoemia and mild hypovolemia, if the diagnosis is uncertain a careful isotonic saline challenge may be the safest first step. Patients with hypovolemic hyponatremia 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 hyponatremia.⁵¹

Conclusion

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

The development of the vaspressin-2 receptor antagonist class of medications gives clinicians the ability to target the underlying pathophysiology of SIAD and hypervolemic hyponatremia. 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 hyponatremia. ■

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