Hyponatraemia: Pathophysiology, treatment and future directions

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CLINICAL POINTS

- The sequelae of hyponatraemia can be varied and devastating, therefore prompt and appropriate correction is vital.
- Hyponatraemia has multiple aetiologies and the cause needs to be determined before the appropriate treatment can be chosen
- Measurement of volume status, serum osmolality, urinary sodium concentration and urinary osmolality are fundamental in order to correctly diagnose the precipitating cause.
- Over-rapid correction of chronic hyponatraemia can have permanent and devastating neurological consequences
- The introduction of new drugs for the treatment of hyponatraemia, the 'Vaptans', which block the vasopressin receptor and cause excretion of free water are an important addition to the options available to the clinician for the treatment of hyponatraemia.

ABSTRACT

Hyponatraemia is the most common electrolyte abnormality in clinical practice. While it may be an incidental discovery or manifest with subtle symptoms such as mild confusion, it can also be associated with severe neurological complications and may even result in death. Mismanagement of hyponatraemia with over-rapid correction of the electrolyte abnormality can cause serious and long-lasting neurological consequences. An understanding of the pathophysiology of hyponatraemia is necessary in order to select the appropriate treatment and avoid the complications associated with this condition and its management. The recent introduction of vasopressin receptor antagonists offers clinicians a new option in the management of this challenging condition.

INTRODUCTION

Hyponatraemia, commonly defined as a serum sodium ≤ 135 mmol/L, is the most frequently encountered electrolyte abnormality in clinical practice[1]. Both the disorder itself and its management can lead to significant morbidity and mortality. Severe hyponatraemia (≤120 mmol/L) developing acutely can result in serious neurological sequelae due to water shift into brain cells, leading to confusion, restlessness, seizures, coma, brainstem herniation, respiratory arrest and even death. These neurological signs and symptoms are usually absent in those in whom hyponatraemia develops gradually due to the ability of brain cells to adapt to the slow change in the tonicity of the extracellular fluid[2].

Patients in whom the development of hyponatraemia is gradual are not always truly asymptomatic, however, and they may have subtle neurological abnormalities that lead to attention deficits and an increased risk of falls[3]. This is crucially important in the elderly, a population at increased risk of both falls and hyponatraemia[4,5]. There is also emerging evidence to suggest that chronic, mild hyponatraemia may result in metabolic bone loss, further increasing the risk of fracture in the elderly patient with chronic hyponatraemia[6]. In hospitalised patients, low serum sodium is an independent risk factor for in-hospital mortality, meaning that regardless of the cause of the hyponatraemia or the co-morbidities present, these patients have a greater mortality risk and this risk increases in proportion with the decrease in their serum sodium concentration[7]. Furthermore, hyponatraemia may be a modifiable risk factor for mortality in congestive heart failure as suggested by the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF) study in which an increase in serum Na^+ of ≥ 2 mmol/L almost halved the mortality rate sixty days post discharge after an exacerbation of congestive heart failure[8]. More research is needed in this area to evaluate the role of serum sodium as a risk factor for mortality in seriously ill patients.

In addition to appreciating the significance of hyponatraemia as it relates to patient outcomes, a thorough understanding of the treatment of this

Osmolality is the number of osmoles of solute per kilogram of solvent

Tonicity is the total concentration of particles which *cannot* freely cross the membrane and therefore induce transcellular shifts of water

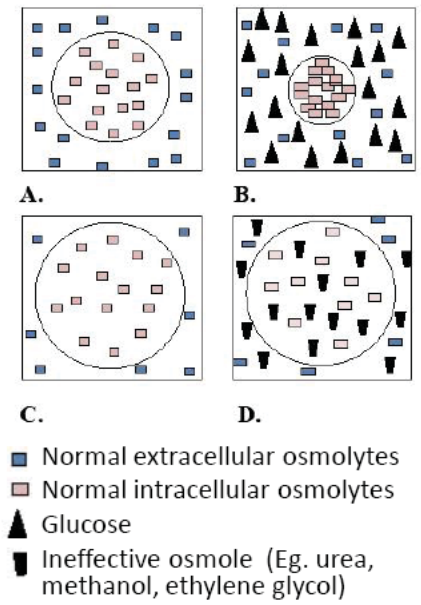
condition is essential to avoid the devastating consequences of mismanagement. Over-rapid correction of long-standing hyponatraemia can result in a demyelination syndrome in the central nervous system (CNS) which destroys CNS structures and leaves the patient with serious, persistent neurological disabilities. Classically, demyelination occurs in the pons resulting in central pontine myelinolysis (CPM) but demyelination due to over-rapid sodium correction can occur anywhere in the CNS[9].

The following paragraphs will explain the pathophysiological mechanism of various types of hyponatraemia and their potential consequences. Moreover, a discussion of the proposed method of correction of each of these conditions will be provided.

PATHOPHYSIOLOGY

Treatment of hyponatraemia in clinical practice firstly involves correctly identifying the cause in order to choose the most appropriate therapy. The causes of hyponatraemia are exceedingly varied and an understanding of the underlying pathophysiology of the condition is of utmost importance. This understanding helps the clinician distinguish a patient who may have hyponatraemia merely from excessive consumption of water from one in whom a subtle electrolyte imbalance is their first presentation of malignancy.

Broadly speaking, hyponatraemia occurs due to an excess of extracellular water relative to extracellular sodium. In order to discuss the causes of this excess in extracellular water, two important terms first need to be defined: osmolality and tonicity. The osmolality of a solution is the number of osmoles of solute per kilogram of solvent. Note that the particles considered in the calculation of the osmolality of a solution may or may not freely cross the cell membrane; that is, this measurement does not confer any information about how the dissolved particles will affect transcellular shifts of water in vivo. The tonicity of a solution, however, is the measure of the total concentration of particles which *cannot* freely cross the membrane and these, therefore, do induce transcellular shifts of water. The causes of the excess in extracellular water that lead to hyponatraemia can be associated with a hypertonic, isotonic or hypotonic



▲ **Figure 1. A. Normal plasma osmolality and tonicity with normal cell size. B. Hypertonic hyponatraemia with cell shrinkage due to hyperglycaemia. C. Hypotonic hyponatraemia with low plasma osmolality. D. Hypotonic hyponatraemia with normal/high osmolality due to th abnormal presence of a substance that can cross the cell membrane.**

extracellular fluid and the treatment of these types of hyponatraemia differs. There is also the case of pseudohyponatraemia, which refers to a laboratory artefact that results in a low sodium measurement in the presence of normal serum sodium[10].

NON-HYPOTONIC HYPONATRAEMIA

Consider first the following types of non-hypotonic hyponatraemia, that is those associated with a hypertonic or isotonic extracellular fluid and pseudohyponatraemia resulting from a laboratory artefact.

HYPERTONIC HYPONATRAEMIA

This can be caused by any solute which remains in the extracellular space and cannot cross the membrane, thereby inducing movement of water out of cells and a decrease in the concentration of the extracellular sodium. A common example of this is the dilution of extracellular sodium that occurs due to the osmotic effect of extracellular glucose in diabetic ketoacidosis. In this condition, glucose cannot enter the cell due to lack of insulin and the high extracellular concentration of glucose therefore draws water out of the intracellular compartment and dilutes the serum sodium (See Figure 1, example B)[11].

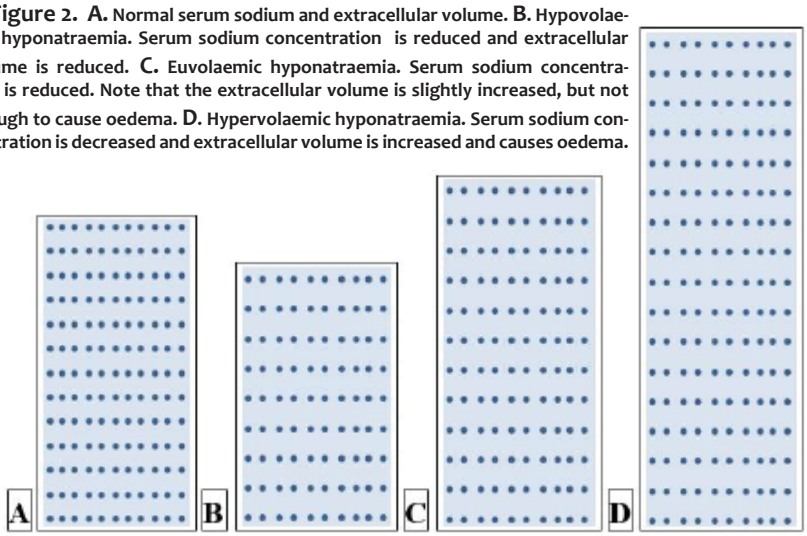
ISOTONIC HYPONATRAEMIA

This situation occurs when there is infusion or absorption of an isotonic solution, such as mannitol, that does not contain sodium. As a result, the measured sodium concentration will be low, but there will be no transcellular shifts in water. Isotonic hyponatraemia can arise following trans-urethral resection of the prostate (TURP) and does not require correction unless there is progression to hypotonic hyponatraemia as substances in the irrigating fluid such as glycine are metabolised to CO_2 leaving free water in the serum[11].

PSEUDOHYPONATREMIA

This occurs when the sodium concentration is measured using methods that allow high serum protein or lipid concentrations to interfere with the interpretation of the result, leading to a falsely low sodium measurement. Pure pseudohyponatraemia does not require any correction of the serum sodium. It does, however, alert the clinician to the presence of a serious derangement in a patient's

Figure 2. A. Normal serum sodium and extracellular volume. **B.** Hypovolaemic hyponatraemia. Serum sodium concentration is reduced and extracellular volume is reduced. **C.** Euvolaemic hyponatraemia. Serum sodium concentration is reduced. Note that the extracellular volume is slightly increased, but not enough to cause oedema. **D.** Hypervolaemic hyponatraemia. Serum sodium concentration is decreased and extracellular volume is increased and causes oedema.



blood lipids or protein concentration and could, for example, suggest a diagnosis of familial hypertriglyceridaemia or multiple myeloma[12].

HYPOTONIC HYPONATRAEMIA

This is, by far, the most common type of hyponatraemia in clinical practice and can be associated with low, normal or increased serum osmolality depending on the cause. Again, determining the serum osmolality will give essential clues to the cause of the hyponatraemia and will guide the treatment required.

Hypotonic hyponatraemia with normal or high serum osmolality occurs when there is a large volume of a solute such as urea, ethanol, methanol or ethylene glycol in the extracellular fluid that can freely cross the cell membrane. These substances contribute to the osmolality but have no effect on the tonicity of the extracellular fluid. Consequently, they do not affect transcellular shifts in water (See Figure 1, example D). This is important as these patients are as much at risk for the complications of a hypotonic extracellular fluid as are patients with hypotonic hypo-osmolar hyponatraemia. This means they are equally at risk of suffering from the osmotic demyelination syndrome as a patient with both low osmolality and low tonicity if their serum sodium is corrected too quickly[11].

Finally, hypotonic hyponatraemia may be associated with low osmolality. The extracellular sodium in this case is diluted by either excessive water intake or, more commonly, by some impairment in the ability of the kidney to excrete excess water. Total body stores of sodium in these patients may be decreased, normal or increased and the sodium stores can be clinically estimated by assessing the volume of extracellular fluid, as will be discussed below[11].

HYPOTONIC HYPONATRAEMIA – EXCESS WATER INTAKE

In this situation, water intake exceeds the maximum diluting capacity of the kidney and thus the kidney cannot correct the serum electrolyte concentrations. The kidney can excrete approximately 17 litres of water per day with a minimum urinary osmolality of 50 mmol/kg. Water consumption in excess of 17 litres per day will therefore result in dilution of the extracellular fluid. This occurs most often in psychiatric disease as psychogenic polydipsia and is also seen following endoscopic surgery in which hypotonic irrigation solutions are used[13].

Psychogenic polydipsia occurs most frequently in patients with schizophrenia and hyponatraemia in these patients is more severe than in a healthy subject for an equivalent water intake. This may be attributed to alterations in the secretion of vasopressin (antidiuretic hormone–ADH), atrial natriuretic peptide (ANP) or both. Vasopressin acts in the collecting duct of the kidney and results in retention of free water. In the presence of a hypotonic extracellular fluid the secretion of vasopressin should be suppressed. ANP also acts on the kidney through multiple mechanisms causing excretion of sodium. In patients with schizophrenia, vasopressin often fails to suppress completely in the presence of hypotonic extracellular fluid and ANP release is stimulated resulting in retention of free water and loss of sodium, respectively, thus exacerbating the effects of excessive intake of free water[14].

TURP and trans-cervical resection of the endometrium (TCRE) are endoscopic surgeries for treatment of benign prostatic hyperplasia and menorrhagia, respectively. Both procedures can require the use of hypotonic irrigating fluid. These hypotonic solutions may be absorbed into the circulation and cause dilution of the extracellular fluid thereby causing a hypotonic hyponatraemia[15]. While excess water absorption in both TURP and TCRE can have serious, even fatal, consequences, the case of TCRE-induced hyponatraemia is especially alarming as menstruating females, for reasons that are as yet unclear, are 25 times more susceptible to permanent brain damage and death than men once cerebral oedema from a sudden fall in serum sodium occurs[16,17].

HYPOTONIC HYPONATRAEMIA – IMPAIRED WATER EXCRETION

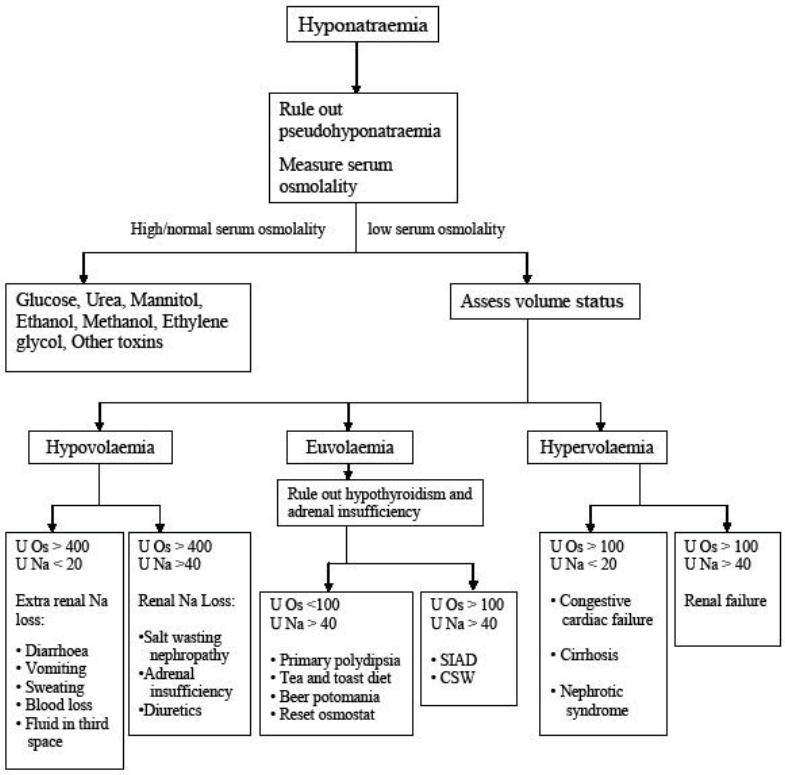
Hypotonic hyponatraemia associated with an impaired ability of the kidney to excrete excess water can be subdivided into hyponatraemia with a hypovolaemic, euvolaemic or hypervolaemic state. In hypovolaemic hypotonic hyponatraemia, total body sodium as well as total body water is low but there is a relative excess of body water leading to dilutional hyponatraemia (See Figure 2, example B). The total body sodium can be reduced by renal sodium loss (for example in adrenal insufficiency, salt wasting nephropathy and diuretic use), extra-renal sodium loss (for example diarrhoea, vomiting, blood loss and excessive sweating) or by sequestration of fluid in a third space (for example burns or peritonitis)[11].

HYPERVOLAEMIC HYPONATRAEMIA

Characterised by high total body sodium and a relative excess of body water leading to dilutional hyponatraemia. This occurs in conditions where the effective circulating volume is reduced and there is secretion of aldosterone and vasopressin in order to stimulate the kidney to retain sodium and water to restore the circulating volume. Such conditions include congestive heart failure (CHF), cirrhosis and nephrotic syndrome. Hypervolaemic hyponatraemia also occurs in renal failure where the kidney loses the ability to excrete excess water (See Figure 2, example D)[11].

EUVOLAEMIC HYPONATRAEMIA

It can be associated with decreased intake of solutes. This often occurs in individuals who are malnourished such as elderly persons who consume a tea-and-toast diet or in beer potomania in which there is regular intake of large amounts of beer with little food consumption. The low intake of solutes impairs the ability of the kidney to excrete water.



▲ **Figure 3** U Os - Urinary osmolality; U Na - Urinary sodium concentration. Adapted from 2,11,23,25.

Hypothyroidism, through multiple mechanisms which are incompletely understood, as well as adrenal insufficiency, through loss of sodium from the kidney due to deficiencies in aldosterone and cortisol, can also cause euvolaemic dilutional hyponatraemia[2]. The syndrome of inappropriate antidiuresis (SIAD), which is caused by inappropriate vasopressin release in the presence of hypotonic extracellular fluid leading to retention of free water by the kidney, is another commonly diagnosed cause of hypotonic euvolaemic hyponatraemia. SIAD has many varied causes ranging from cancers, CNS disorders, drugs, pulmonary conditions, human immunodeficiency virus, pain, nausea and the post-operative state (See Figure 2, example C)[18].

DIAGNOSIS

The symptoms of hyponatraemia depend on the degree of the hyponatraemia and the speed with which it develops. The most serious manifestations of hyponatraemia occur when serum sodium is rapidly (within 48 hours) and severely reduced (<120mmol/L). Symptoms include confusion, hallucinations, seizures, coma, and death. Conversely, chronic mild hyponatraemia may be asymptomatic, or may have subtle symptoms such as poor concentration[3,11].

Patients presenting with symptoms that could result from hyponatraemia should be questioned about conditions that lead to derangements of serum sodium concentration in their medical history. It is evident from the extensive range of types and causes of hyponatraemia that all elements

of the medical history are of utmost importance since long-standing or recent illness, psychiatric illness, medications, recent surgery and poor social circumstances may either cause or exacerbate the condition.

Once a diagnosis of hyponatraemia has been confirmed by a serum sodium level, the aetiology needs to be confirmed. The cornerstone tests used in the differential diagnosis of hyponatraemia are serum osmolality, urine sodium and urine osmolality. These simple tests help classify the hyponatraemia as discussed above and allow the clinician to identify the cause of the hyponatraemia and thereby choose the appropriate treatment[2].

A step-by-step approach to elucidating the cause of hyponatraemia first begins with ruling out pseudohyponatraemia by checking total serum protein and a lipid profile (See Figure 3). Serum osmolality should then be considered. If it is normal or high, substances such as glucose and urea in the serum that can increase the osmolality, should be sought (use of the osmolal gap at this point has been shown to be unhelpful; for further discussion see references 19-21). It is useful to remember that if the osmolality is normal or high the tonicity may be low, normal or high depending on the nature of the substance that is causing the increase in the osmolality of the extracellular fluid. A low osmolality, however, always implies a low tonicity[2].

If serum osmolality is low, the volume status, which is an indication of total body sodium stores, should be established. Many of the traditional clinical signs of hypovolaemia such as sunken eyes and dry mucous membranes, have very poor sensitivity and specificity, but the presence of dry axillae is a good clinical indication of hypovolaemia and low total body sodium. Hypervolaemia is most reliably indicated by measurement of the jugular venous pressure[22]. To increase accuracy, these clinical parameters can be combined with measurements of serum urea (low in hypervolaemia and SIAD, high in hypovolaemia) and serum uric acid (normal or high in hypovolaemia except in renal salt wasting where levels are surprisingly low; low in SIAD)[23]. If the patient is found to be hypovolaemic, the urine sodium concentration can help reveal the underlying cause. In all cases of hypovolaemia, with the exception of renal salt wasting, the kidney will avidly retain sodium and the urinary sodium will be less than 20 mmol/L (urine sodium <20mmol/L is a sensitive indicator of decreased circulating volume)[2].

The presence of a euvolaemic state can be confirmed by a urinary sodium measurement of > 40 mmol/L, assuming sufficient dietary salt intake. The causes of euvolaemic hyponatraemia can be further differentiated by measuring the urinary osmolality. The urinary osmolality will be low, that is the urine will be maximally dilute, in conditions where there is appropriate suppression of vasopressin such as in primary polydipsia. Conversely, urine will be less than maximally dilute in SIAD and cerebral salt wasting (remember that urinary osmolality is made up of many osmolytes other than sodium so there is no direct relationship between urinary sodium and urinary osmolality)[2,24].

In hypervolaemic patients, the urinary sodium again helps to differentiate the cause. Renal failure in hypervolaemic patients is suggested by a urinary sodium of >40 mmol/L. Other causes of hypervolaemia (CHF, cirrhosis, nephrotic syndrome) will result in a decreased effective circulating volume and avid retention of sodium by the kidney through the renin-angiotensin-aldosterone system[2,25].

TREATMENT

There is not a single, proven strategy for the treatment of hyponatraemia[11]. However, irrespective of the treatment modality chosen, in the case of symptomatic hyponatraemia in which correction is critical to avoid neurological damage, it must increase serum sodium with sufficient speed in order to prevent serious neurological sequelae while avoiding the devastating effects of osmotic demyelination. When hyponatraemia presents with less severe symptoms, correction is still necessary but it can be achieved over a longer time period as the immediate risks of severe neurological damage due to the hyponatraemia are not present.

Osmotic demyelination occurs with the over-rapid correction of long-standing hyponatraemia (>48 hours). The significance of the risk of osmotic demyelination cannot be overestimated. Sodium correction of >12mmol/L/24 hours, or in some reported cases as little as 10 mmol/L/24 hours[26], can result in central pontine demyelination. This condition leads to multiple neurological deficits including

$$\text{Change in serum sodium} = \frac{\text{infusate}^{*}\ Na^{+} - \text{serum } Na^{+}}{\text{Total body water}^{\dagger} + 1}$$

*Normal saline infusate Na^{+} = 154 mmol/L
Hypertonic saline (3%) infusate Na^{+} = 513 mmol/L

† Total body water in non-elderly women = body weight in kilograms x 0.5
Total body water in non-elderly men = body weight in kilograms x 0.6
Total body water in elderly women = body weight in kilograms x 0.45
Total body water in elderly men = body weight in kilograms x 0.5

Figure 4. Calculating infusion rate in symptomatic hyponatraemia. Adapted from 11,29.

dysarthria, dysphagia, quadriparesis, pupillary and occulomotor abnormalities. Osmotic demyelination can also occur outside the pons resulting in a huge variety of lesions in structures such as the cerebellum, external capsule, hippocampus, putamen, cerebral cortex, thalamus and caudate nucleus[27].

Certain populations are more at risk for osmotic demyelination syndromes. These include alcoholics, malnourished populations, those with prolonged use of diuretics as well as patients post-liver transplant. It should be emphasized, however, that regardless of the aetiology of the chronic hyponatraemia and the method used to correct it, there is always a risk of osmotic demyelination with rapid correction of hyponatraemia[27]. This review focuses on the treatment of the most common type of hyponatraemia encountered – hypotonic hyponatraemia.

Symptomatic hypotonic hyponatraemia with euvolaemia or hypervolaemia and *concentrated* urine should be treated with hypertonic saline until such time that either i) the symptoms have resolved ii) the serum sodium is >130mmol/L or iii) the serum sodium has been increased by a total of 18mmol/L. Associated hypothyroidism and cortisol deficiency should be treated concurrently as appropriate. (Note that autocorrection of hyponatraemia can result from treatment of these conditions without the addition of saline or water restriction so these patients are at particular risk for inadvertent rapid correction of the serum sodium and osmotic demyelination). The serum sodium may be increased by 1-2 mmol/L for several hours in patients with severe symptoms, but total correction in 24 hours should ideally be kept below 8 mmol/L. This should be feasible, as small increases in serum sodium substantially decrease cerebral oedema and alleviate symptoms[28]. There are several formulae available to calculate the speed and concentration of the infusion necessary to achieve a controlled increase in serum sodium and one example is given in Figure 4. This formula calculates the magnitude of the change in serum sodium with infusion of 1 full litre of infusate. The litre of fluid should be given over a sufficient amount of time so that the hourly increment in sodium concentration does not exceed 1–2mmol/L/hour[29]. Furosemide – a loop diuretic – may be administered along with hypertonic saline to avoid excessive volume expansion[28].

Patients with hypervolaemia and *concentrated* urine with less severe or no symptoms and patients with hypotonic euvolaemic hyponatraemia with dilute urine can be treated with water restriction (usually < 800mL/day) and close observation. Severe symptoms (for example seizures or coma) may call for the use of hypertonic saline in those with dilute urine. Water restriction in these cases needs to be closely monitored as water restriction carries the same risk of osmotic demyelination as the use of hypertonic saline[28].

Hypovolaemic hypotonic hyponatraemia can almost always be managed with isotonic saline[2]. Patients with hypovolaemic hypotonic hyponatraemia associated with the use of thiazide diuretics use should stop the drug and it should not be reintroduced as the hyponatraemia is likely to return with reintroduction of the drug[30].

Details of the long-term management of hypotonic hyponatraemia is beyond the scope of this article but broadly speaking SIAD is traditionally managed by removing any inciting cause as well as restricting water intake. Hypervolaemic hypotonic hyponatraemia is more effectively managed with salt restriction and diuretics (with the exception of renal failure where fluid restriction is necessary)[28].

VAPTANS

The recent introduction of vasopressin antagonists, the 'vaptans', offers clinicians new options for the management of hyponatraemia. These drugs work by antagonising the vasopressin receptor in the medullary collecting duct (V_2R) of the kidney. This halts insertion of water channels and leads to increased excretion of free water. The first of these drugs, conivaptan, approved by the FDA in 2005, has been approved for short-term in-patient intravenous use. It is restricted to inpatient use due to its potent inhibition of the cytochrome P450 isozyme CYP 3A4 and subsequent potential for serious drug interactions. Its action is not confined to the V_2R as it antagonises vasopressin receptors on blood vessels, platelets and the myocardium, increasing the potential for adverse effects[28,31-2]. This drug's ability to antagonise such a wide range of receptors may have advantages, however, and current research is exploring the potential use of conivaptan in congestive heart failure where antagonism of vasoconstriction and increased platelet adherence mediated by vasopressin may be advantageous[33-4].

In contrast to conivaptan, the newly approved tolvaptan is V_2R selective. It is available as an oral preparation and exhibits fewer CYP 3A4 interactions. It is indicated for the treatment of hypervolaemic and euvolaemic hyponatraemia with inappropriately concentrated urine where the serum sodium concentration is <125 mmol/L or where the patient is symptomatic and has resisted correction with fluid restriction[35-6]. As it is an oral preparation with fewer drug interactions it is suitable for outpatient use. However, as with all methods of correcting hyponatraemia, initial correction must

be closely monitored and the patient should be admitted to hospital for this[28].

An understanding of the pathophysiology of hyponatraemia makes the indications for the use of the vaptans clear. In situations where there is *inappropriate* concentration of urine, that is where the total body water is normal or increased, the vaptans can be used to encourage the excretion of free water by the kidney in order to increase the sodium concentration. There is no role for the vaptans in conditions where urine is appropriately concentrated, such as in dehydration, or where the sodium is low due to increased water or decreased solute intake. Finally, the role of vaptans in the treatment of acute severe hyponatraemia that is unsuitable for a trial of water-restriction has yet to be defined.

CONCLUSION

Hyponatraemia is a common electrolyte imbalance with an aetiology that is still imperfectly understood. It can be associated with a large spectrum of neurological complications ranging from mild, reversible cognitive deficits to permanent and devastating neurological disability. The cause of the drop in serum sodium must be accurately determined in order to choose an appropriate and safe treatment. Once the diagnosis is made, striking the balance between adequate and dangerous correction still poses a significant challenge. The introduction of vasopressin antagonists has been a significant advancement in the management of the condition. This treatment option, along with ever-expanding knowledge of the complex physiology underlying sodium homeostasis, promises to improve the outlook for patients with hyponatraemia in future years.

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