

Guidelines Review

Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations

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Plasma sodium is one of the most commonly measured analytes in laboratory medicine and hyponatraemia is frequently observed, occurring in 15–30% of hospital patients. Severe hyponatraemia is important because of its associated mortality and morbidity risks, and because its treatment also carries the risk of severe morbidity. Nevertheless, it is a complex subject and our understanding of its pathophysiology is incomplete. Although many authors have published in the area there is little in the way of evidence-based guidelines, and, except for part of a recent publication,¹ no Australasian guidelines on diagnosis or management that this author could find.

In 2007, a panel led by Joseph Verbalis published a review of the diagnosis and modern treatment of hyponatraemia with the title given above.² While the review was mainly concerned with therapeutic aspects, the pathophysiology and diagnosis of hyponatraemia were extensively discussed as well. It highlighted the role of anti-diuretic hormone (arginine vasopressin, AVP) secretion, appropriate or otherwise, in almost all forms of hyponatraemia, and the possible applications of AVP antagonist therapies in these conditions; in this regard it is noted that the authors declared interests in several pharmaceutical companies developing these treatments. Nevertheless, the diagnostic pathway they advocated was 'classical', and the pathophysiology of newer entities was well described. So the question is: are these guidelines likely to help the clinical biochemist grappling with the complexities of hyponatraemia?

Classification and Pathophysiology

In classifying the hyponatraemias, the paper starts with the need to distinguish hypotonic from non-hypotonic hyponatraemia, by measurement of plasma osmolality. Non-hypotonic hyponatraemia may be due to 'pseudohyponatraemia', in which the space-occupying effect of high concentrations of lipid or protein effectively reduces the amount of plasma water, and hence sodium, introduced into the measurement

cell; the measured osmolality is probably normal in this case. Alternatively it is due to the presence of high concentrations of osmotically active substances, for example glucose, mannitol or radiographic contrast media, which tend to draw water out of cells; in this situation the measured osmolality is probably high. Surprisingly perhaps, the paper omits to mention the use of direct sodium measurement in pseudohyponatraemia. However, it does mention that it is possible to calculate the sodium concentration that would have been obtained in the absence of hyperglycaemia.

The hypotonic hyponatraemias are then classified according to the clinical assessment of fluid status, aided by spot urine sodium measurement, into hypovolaemic, euvolaemic and hypervolaemic categories. Hypovolaemia, or reduced extracellular fluid volume, is diagnosed by its clinical signs and by plasma urea, creatinine, uric acid and, most usefully, by spot urine sodium concentration. (Interestingly, a recent paper reported that the fractional excretion of sodium, FENa, which is a more sophisticated measure of renal sodium handling, was not as accurate as the spot urine sodium concentration for making this distinction.³)

The main causes of depletion hyponatraemia involve loss of body fluid from the gastrointestinal or urinary tracts. Increased AVP concentrations are usual, due to the baroreceptor reflex designed to maintain extracellular volume. Thus, despite the hyponatraemia, the AVP concentrations are 'appropriate'. In hyponatraemia due to diarrhoea or vomiting, fluid loss is often accompanied by ingestion of hypotonic fluids; in the presence of AVP this leads to relatively more retention of water than of sodium, and hyponatraemia results. Regarding thiazide diuretics, the authors cite evidence of abnormal thirst and water intake in those affected by hyponatraemia. In cerebral salt wasting, hypovolaemia is due to renal loss of sodium and water following head trauma or brain surgery; it is not clear whether neural pathways, natriuretic peptides

or both are involved in this. Again, the hypovolaemia stimulates AVP secretion leading to relative water retention and hyponatraemia. This condition shares many biochemical characteristics with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which may make the differential diagnosis difficult. Mineralocorticoid deficiency also causes hypovolaemia through urine sodium wasting, with secondary AVP-mediated water retention contributing to the hyponatraemia; in this case though, hyperkalaemia is marked and urine potassium is low, which are indicative of the diagnosis.

The authors point out the limitation of urine sodium in cases of vomiting, in which metabolic alkalosis may cause bicarbonaturia, in turn forcing urine sodium to exceed 30 mmol/L despite hypovolaemia; this is one of the recognised situations in which urine chloride measurement is helpful. However, thiazides, cerebral salt wasting and mineralocorticoid deficiency all cause natriuresis, so that the urine sodium will be unreliable for this purpose in these conditions too. Thus, as the authors point out, the urine sodium is expected to be below 30 mmol/L when fluid losses are non-renal in nature, for example in diarrhoea, vomiting without alkalosis or loss into the peritoneum or tissues.

Euvolaemic hyponatraemia is diagnosed when there is no clinical or biochemical evidence of volume depletion or expansion. These conditions include SIADH, glucocorticoid deficiency, hypothyroidism, the nephrogenic syndrome of inappropriate antidiuresis, exercise-associated hyponatraemia, primary polydipsia and, occasionally, hyponatraemia due to low solute intake. In the first three of these, high AVP concentrations drive renal water retention. The diagnostic criteria for SIADH have changed little since it was first described and are discussed in the review; the authors stress that a urine osmolality greater than 100 mmol/kg is indicative of AVP action, and is therefore 'inappropriate' in the setting of euvolaemic hyponatraemia. Nevertheless it is a diagnosis of exclusion. The paper includes a long list of conditions associated with SIADH, which includes cerebral and pulmonary diseases, tumours and various drugs. Glucocorticoid deficiency (due to pituitary failure) is associated with inappropriately measurable AVP concentrations causing water retention (normally, cortisol inhibits AVP secretion⁴). In hypothyroidism, hyponatraemia seems associated only with the severest states of myxoedema; impaired cardiac function causes baroreceptor-mediated AVP secretion and water retention.

AVP-independent causes of euvolaemic hyponatraemia are recognised, however. The rare nephrogenic syndrome of inappropriate antidiuresis is due to an activating mutation in the AVP receptor, causing water retention in the absence

of AVP. (A case report from New Zealand of a patient with this condition was published recently.⁵) Exercise-associated hyponatraemia and polydipsia seem to cause hyponatraemia primarily by excess water ingestion; AVP secretion, due to stress, drugs or psychiatric disease may also be involved. Low solute intake, for example in beer potomania, causes hyponatraemia in the absence of AVP due to the kidney's inability to dilute urine to osmolality below about 50 mmol/kg, resulting in obligatory retention of water.

Hypervolaemic hyponatraemia is associated with clinically detectable oedema, the main conditions being heart failure, cirrhosis, renal failure and the nephrotic syndrome. In heart failure, poor cardiac output leads to increased AVP-mediated water retention and increased beta-adrenergic stimulation of renin release and renal tubular sodium retention. Interestingly, although the secretion of natriuretic peptides also increases markedly in heart failure, their physiological action, which would normally counter that of the renin-angiotensin-aldosterone system, is attenuated because of other changes that occur in this condition.⁶ In the hyponatraemia associated with cirrhosis, AVP secretion is increased, but the authors are less clear on the stimulus for this. The liver fibrosis leads to portal hypertension and to increased blood flow in the splanchnic system but reduced blood flow in the peripheral circulation.⁷ As in cardiac failure, there is renin release, sodium retention and non-osmotic AVP release with the net effect of hyponatraemia. The involvement of AVP is confirmed by studies in which AVP antagonists caused increase of both water excretion and serum sodium concentration when given to patients with cirrhosis. Hyponatraemia in the nephrotic syndrome is associated with severe hypoalbuminaemia (plasma albumin less than 20 g/L), when hypovolaemia may occur, which may lead to AVP secretion and water retention.

Treatment of Hyponatraemia

Before reviewing the treatment of hyponatraemia, the authors examined the issue of the rate of correction of hyponatraemia. Because acute changes in plasma sodium concentration can cause movement of water down its osmotic gradient into cells, and the brain is confined within the space of the skull, acute hyponatraemia can cause severe neurological symptoms (for example, nausea, malaise, headache, disorientation, seizure, coma and even death⁸). However if hyponatraemia develops slowly, brain cells adapt by extruding organic solutes, thus minimising the difference in osmolality across the cell membrane and preventing the cerebral oedema. By the same token, rapid partial correction of acute onset hyponatraemia generally relieves symptoms, whereas rapid correction of chronic hyponatraemia results in osmotically-driven movement of water out of brain cells, cell shrinkage and the osmotic demyelination syndrome. In this condition, severe

neurological deficits appear several days after the onset of treatment and for some patients these are permanent. Based on several reviews, the authors therefore strongly recommend that the rate of correction of chronic hyponatraemia is limited to less than 10 to 12 mmol/L in the first 24 hours and to 18 mmol/L over 48 hours.

Bearing this in mind, the recommended treatments for hyponatraemia depend on the rate of onset and the cause of the hyponatraemia. For depletional hyponatraemia the basic therapy is fluid replacement with normal saline. For euvolaemic hyponatraemia, the treatment involves treating any immediate cause, such as hormone replacement; if this is not feasible, water restriction is recommended, possibly with some hypertonic saline or AVP antagonist therapy such as demeclocycline. The authors also mention a new class of agent, the κ -opioid receptor agonists, which act to suppress AVP secretion and to promote water excretion in patients with cirrhosis,⁹ however, these are not discussed further. Symptomatic patients may need hypertonic saline infusion, which should continue only long enough to relieve symptoms, to raise plasma sodium to a safe level (approximately 120 to 125 mmol/L) or until plasma sodium has increased by 18 mmol/L. Basic treatment of hypervolaemic hyponatraemia is with fluid restriction, diuretics and sodium restriction. In each case, if the hyponatraemia has been long-standing, the rate of correction may need to be controlled, necessitating frequent plasma sodium measurements.

The final section of this paper reviewed some newer pharmaceutical agents, not yet available in Australia, having direct antagonistic activity against AVP receptors. There are three types of AVP receptor, 1a, 1b and 2, with different locations, second messenger systems and functions. The renal AVP receptor is type 2, which is also present in the vascular endothelium, and its activation is mediated via cyclic AMP. The type 1 receptors mediate vasoconstriction, platelet activation, myocardial function and ACTH secretion and these receptors use the phospholipase C system as second messenger. The first of the non-peptide vasopressin receptor antagonists (known as 'vaptans') was conivaptan, which is active against both type 1a and 2 receptors; later agents, such as tolvaptan are specific for the type 2 receptor. The vaptans have been shown to be active in causing free water loss, or aquaresis, when used in SIADH and congestive heart failure in short-term trials. However, in a heart failure study, no mortality benefit was shown, so the main clinical benefit in this setting may be reduction in use of diuretics. Available data suggest that they will remain effective in longer-term treatment. So far, osmotic demyelination syndrome has not been a problem, but this may be because the drugs have been used in carefully controlled clinical trial situations. Clearly these agents are

probably contra-indicated in depletional hyponatraemia, as the AVP secretion is beneficial in these conditions, highlighting that the diagnosis of euvolaemic hyponatraemia needs to be secure before these agents can be used. Whether these agents enter clinical use in Australia remains to be seen.

Summary and Conclusions

This paper reviews the classification, differential diagnosis and standard treatment of the hyponatraemias, and offers a view on the intriguing newer therapeutic approach using vaptans. While it appears to summarise the relevant literature well, it is not a systematic review carried out according to the principles of evidence based medicine. Particularly bearing in mind the declared commercial interests of the authors and the relative absence of randomised controlled diagnostic studies, most of the opinions expressed need to be seen as based on expert opinion, rather than on higher quality evidence. Nevertheless, the review explains the pathophysiology of the hyponatraemias, updates the knowledge of more recently discovered clinical conditions and highlights areas of uncertainty that remain to be explained. For a topic that causes difficulty for many, (well it did for me!), this review should assist in increasing the understanding of this complex, yet common and still fascinating condition.

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