Hyponatremia: A role for vasopressin receptor antagonists?

Hyponatremia, defined as a serum sodium of <135 mmol/l, is the most frequently encountered electrolyte disturbance in clinical practice, estimated prevalence is 15–20% of all hospital inpatients.[1]

Hypotonic hyponatremia with serum osmolality <275 mosm/kg is responsible for symptoms ranging from mild headache, nausea and gait disturbance to altered mentation seizures and coma depending on severity. Caused usually by a relative increase in renal water reabsorption due release of arginine vasopressin (AVP), hyponatremia can occur with hypovolemia, hypervolemia, or euvolemia.[2] Occasionally, it is caused by excessive consumption or absorption of hypotonic fluid as in polydipsia and TURP syndrome. Acute hyponatremia develops within 48 h and carries a worse prognosis as the brain has little time to adapt.[1,3] It can be fatal unless treated urgently. Chronic hyponatremia occurs over a longer period (>48 h) and is the more prevalent form of the disorder.

Physiological triggers for AVP release are increase in osmolality and decrease in circulating blood volume. When there is hypovolemia, AVP will continue to be secreted even if the osmolality is low, resulting in water retention out of proportion to Na retention and giving rise to hypovolemic hyponatremia. Common causes of this condition are extrarenal losses – gastrointestinal, transdermal; third spacing of fluids as in pancreatitis; renal losses due to diuretics - especially thiazides, salt wasting nephropathies, cerebral salt wasting syndromes, and mineralocorticoid deficiency.

High extracellular fluid states, such as congestive heart failure, liver cirrhosis, or nephrotic syndrome, trigger increased AVP secretion due to low effective circulating volume that overrides osmolality resulting in hypervolemic hyponatremia.

Euvolemic hyponatremia occurs in conditions such as primary polydipsia, glucocorticoid deficiency, hypothyroidism, and beer potomania, but the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause where AVP secretion is inappropriately high without any physiological triggers. Criteria for diagnosis of SIADH were originally defined by Barter and Schwartz in 1967.[4] General anesthesia, nausea, pain, and stress as well as a variety of drugs including opiates nonsteroidal anti-inflammatory drugs and proton-pump inhibitors can cause SIADH. The most frequent causes of SIADH include cancers, particularly small cell carcinoma of the lung, diseases of the lung–pneumonia tuberculosis, asthma intermittent positive pressure ventilation, and central nervous system disorders, e.g., subarachnoid hemorrhage, head trauma, and stroke.

In this issue of JOACP, Rajan et al. describe their use of vasopressin receptor antagonists (VRA), conivaptan and tolvaptan, in postoperative hyponatremic patients. It would have been interesting to know what percentage of their patients developed hyponatremia and how many were on diuretics or drugs known to precipitate SIADH. Since the onset of symptoms were third to sixteenth day postop, one could assume that hyponatremia did not develop acutely. However, they were symptomatic. The recommended first line of treatment in patients with severe or moderately severe symptoms and serum sodium <129 mmol/l is hypertonic saline infusion along with supportive care. Estimation of serum sodium is required at frequent intervals, targeting 1 mmol/l rise per hour to a max of 5 mmol/l or resolution of symptoms, and limiting the increase to <10 mmol/24 h.[1,5]

Subsequently and in mildly symptomatic/asymptomatic patients, volume status needs to be determined to guide management. Hypervolemia is recognized readily, however, difficulty may arise in distinguishing euvolemia from hypovolemia clinically. Hypovolemic patients of non-renal etiology will have urinary sodium <30 mmol/l with osmolality >100 mosm/kg, whereas euvolemic hyponatremia will have urinary Na >30 mmol/l, and the osmolality is >100 mosm/kg unless excess water intake is the cause. These parameters were not measured in the study. When there is doubt, a trial of 500–1000 ml 0.9% saline infusion over 1–2 h helps differentiate. Sodium levels will improve in hypovolemia but will worsen in SIADH as most of the water is retained but the sodium is excreted in a small volume of urine.

In euvolemic hyponatremia presence of underlying kidney disease or diuretic usage is determined. Also, whether the patient is cortisol deficient or hypothyroid – important considerations in the post-operative period, particularly after head and neck surgery. Once these easily addressed causes are ruled out, SIADH remains as diagnosis of exclusion.[1,3]

Hypovolemic hyponatremia requires isotonic fluid infusion and removal of cause. VRAs are contraindicated as they would increase fluid loss and worsen hypovolemia.[3,4]
In the hypervolemic and euvolemic hyponatremia, VRAs have a role but are advocated as second line. Fluid restriction to 500 ml less than urine output in 24 h and removal of precipitating cause are the initially recommended treatment. In addition, loop diuretics and/or spironolactone are recommended in the hypervolemic variety.\textsuperscript{[3,6]}

When this fails to achieve rise in serum sodium of 3–6 mmol/24 h, VRAs are given as second line while simultaneously removing all fluid restrictions to keep the sodium rise within limit.

Over-correction needs to be promptly reversed with plain water intake orally or D5W infusion to keep the sodium rise within 8 mmol/24 h. Some advocate a lower figure of 6 mmol/24 h so as to prevent osmotic demyelination syndrome (ODS).

The American guidelines advocate use of VRAs in non-severe euvolemic or hypervolemic hyponatremia if fluid restriction fails; however, European guidelines do not recommend their use in SIADH and discourage its use in congestive heart failure as well as liver cirrhosis, citing lack of hard evidence and liver toxicity.\textsuperscript{[1,3,7]}

Few key points need to be remembered when using VRAs. They are contraindicated in hypovolemic hyponatremia as the volume depletion will be aggravated. They should not be used after hypertonic saline infusion as dramatic increases in serum sodium can occur, precipitating ODS.\textsuperscript{[4]} VRAs are recommended second line of treatment for euvolemic and hypervolemic hyponatremia of most causes. Fluids should not be restricted when using VRAs. The drug can be discontinued once the cause is removed and hyponatremia resolved. Tolvaptan is widely available, very effective but expensive.

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