Chapter 134

Newer Insight in the Management of Hyponatremia: Role of Aquaretics/Vaptans

Mujahid Beg

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality seen in hospitalized and critically ill patients. It is seen in 15–30% of hospitalized patients. Hyponatremia has been shown to be an independent predictor of mortality in intensive care unit. Even mild asymptomatic hyponatremia has been shown to be associated with attention impairment, falls, fractures and osteoporosis in elderly patients. Conventional management of hyponatremia includes step-by-step management starting from water restriction in mild cases to administration of saline in symptomatic cases. In this article, we will summarize the diagnostic approach to hyponatremia, conventional treatment of hyponatremia as well as future prospective in the management of hyponatremia including the role of aquaretics or vaptans.

CLINICAL FEATURES

Acute hyponatremia (defined as hyponatremia developing within 48 hours) causes lethargy, confusion, psychosis, reversible ataxia when severe it can also cause seizures, coma and respiratory arrest. Chronic and mild hyponatremia can be asymptomatic or it can present with cognitive impairment, falls and weakness.

DIAGNOSTIC APPROACH AND CAUSES OF HYponATREMIA

Falsely low sodium levels can be seen in the setting of hyper-lipidemia and hyperproteinemia, this falsely low sodium levels is referred to as pseudohyponatremia. This pseudohyponatremia is a benign finding and must be excluded before further workup. Presence of osmotically active substances like glucose or mannitol can also cause hyponatremia, but hyponatremia in this case have high serum osmolarity.

Hyponatremia with low serum osmolarity (hypo-osmolar hyponatremia) can occur in the setting of decreased extracellular fluid (ECF) volume (hypovolemic hyponatremia), it can occur in the setting of normal ECF volume (euclidean hyponatremia) or it can occur in the setting of increased ECF volume (hypervolemic hyponatremia).

Another important evaluation apart from serum osmolality and ECF volume status is the measurement of urinary osmolality. If urinary osmolality is less than 10 mOsm/L then cause of hyponatremia can be excessive water intake, reset osmostat or low solute intake.

In hypovolemic hyponatremia, there is decrease in both total body sodium and water leading to ECF volume depletion with consequent AVP release and decreased solute-free water excretion. Clinically the patient will have tachycardia, orthostatic hypotension and loss of skin turgor. Causes of hypovolemic hyponatremia can be further classified into extrarenal and renal causes. Extrarenal causes include vomiting, diarrhea, burns, peritonitis and pancreatitis etc. Renal causes include use of thiazide diuretics, mineralocorticoid deficiency and salt wasting nephritis. Extrarenal and renal causes can be differentiated with the help of estimating urinary sodium; if urinary sodium is less than 10 mmol/L, then this point toward an extrarenal cause and if urinary sodium is more than 20 mmol/L, it points toward a renal etiology of hyponatremia.

Prototype example of euclidean hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH); in this syndrome, there is hyponatremia along with hypo-osmolarity; physical examination did not show any signs of dehydration or fluid overload; urinary osmolality is more than 100 mOsm/L and urinary sodium is more than 25 mmol/L. But, disorders like hypoparathyroidism, hypopituitarism, and adrenal insufficiency must be ruled out before making the diagnosis of SIADH. Causes of SIADH include neoplastic, vascular, infectious and inflammatory disorders of central nervous system (CNS) and respiratory system, drugs like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, carbamazepine, desmopressin and oxytocin can also cause SIADH.

Causes of hypervolemic hyponatremia include cardiac failure, liver cirrhosis and nephrotic syndrome. In these conditions decreased effective arterial blood volume leads to activation of renin angiotensin aldosterone (RAAS) system and increased AVP levels leading to retention fluid in excess to sodium.

Algorithm for diagnostic approach to hyponatremia is shown in Flow chart 1.

CONVENTIONAL TREATMENT OF HYponATREMIA AND ITS DISADVANTAGES

Hyponatremia in hypovolemic patients is treated with infusion of normal saline. The options for treatment of euclidean hyponatremia and hypervolemic hyponatremia are fluid restriction, 3% saline administration and use of loop diuretics. For fluid restriction to be effective, the daily fluid intake should be less than urinary output plus daily insensible losses. Water restriction is slow to work and difficult to sustain due to inherent increased thirst sensation in these patients resulting in poor compliance. Saline administration can also be problematic in patients with hypervolemic hyponatremia as it can further cause volume expansion. Also patients with
hyponatremia of more than 48 hours duration are at an increased risk of developing central or extra pontine myelinolysis if serum sodium is corrected at a rate of more than 12 mmol/L/day. Loop diuretics are effective in hypervolemic patients but they can lead to volume depletion. Demeclocycline is a tetracycline antibiotic has been used to treat chronic hyponatremia as it causes AVP resistant diabetes insipidus like state. The main disadvantage of demeclocycline is nephrotoxicity especially in the presence of liver diseases and congestive heart failure (CHF). Lithium can also increase sodium levels by creating a diabetes insipidus like state, but lithium has a very narrow risk benefit ratio and an array of adverse effects.

ROLE OF VAPTANS/AQUARETICS IN MANAGEMENT OF HYPONATREMIA

Vaptans are vasopressin receptor antagonists, they acts by increasing electrolyte free-water excretion and thereby increasing serum sodium concentration. Recently, nonpeptide antagonists to V2 vasopressin receptor have been developed.

There are specific nonpeptide antagonists namely tolvaptan, lixivaptan and satavaptan, as well as dual V1/V2 receptor antagonist namely conivaptan. But, out of these agents only conivaptan and tolvaptan are approved so far by United States, Food and Drug Administration (FDA). Conivaptan is approved for intravenous use in hospital settings for the treatment of euvolemic and hypervolemic hyponatremia. Velez et al. conducted a retrospective study on 18 patients of SIADH who were treated with intravenous conivaptan, they found that 24 hours after initiation of therapy, all patients had at least a 3 mmol/L increase in serum sodium, with 66.7% (12/18) of the patients having an absolute increase more than or equal to 4 mmol/L, urine osmolality decreased in all patients with a mean reduction of 45.9 ± 28.8% from baseline. They therefore concluded that intravenous conivaptan is an effective aquaretic to treat hyponatremia caused by SIADH.

Tolvaptan is an orally active selective V2 receptor antagonist; it is approved for the treatment of euvolemic and hypervolemic hyponatremia. In two multicenter, randomized, double-blind, placebo-controlled trials (the Study of Ascending Levels of Tolvaptan (SALT) in hyponatremia, SALT-1 and SALT-2), the efficacy of tolvaptan was evaluated in patients with euvolemic or hypervolemic hyponatremia, it was found that serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 days (P < 0.001) and after the full 30 days of therapy (P < 0.001). The condition of patients with mild or marked hyponatremia improved (P < 0.001 for all comparisons). During the
ROLE OF VAPTANS IN SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

In a recent study, hyponatremic patients in the SALT-1 and SALT-2 studies with a diagnosis of SIADH were identified based on clinical diagnosis by individual study investigators. Subjects were randomized to receive oral placebo (n = 52) or tolvaptan 15 mg daily, with further titration to 30 and 60 mg daily, if necessary, based on the response of serum sodium (n = 58). It was found that in patients with SIADH, improvement in serum sodium was significantly greater (P < 0.0001) with tolvaptan than placebo over the first 4 days of therapy as well as the entire 30-day study, with minimal side effects of increased thirst, dry mouth and urination. Only 5.9% of tolvaptan-treated patients had overly rapid correction of hyponatremia as defined by current guidelines. After discontinuation of tolvaptan, serum sodium declined to values similar to placebo.

OTHER VAPTANS

Lixivaptan

Wong et al. conducted a study to investigate the efficacy and safety of three different doses of the V2 receptor antagonist lixivaptan. Forty-four hospitalized patients were included in this study out of them 33 were having cirrhosis. Six were having CHF and 5 were having SIADH. They were randomized to receive 25 mg, 125 mg and 250 mg twice daily of lixivaptan or placebo. It was found that lixivaptan produced a significant overall aquaretic response compared with placebo, with significant dose related increases in free water clearance (P < 0.05) and serum sodium (P < 0.05), without significant changes in orthostatic blood pressure or serum creatinine levels. High dose was of lixivaptan, i.e. 250 mg twice daily experienced increased thirst and dehydration. Gerbes et al. investigated the effect of lixivaptan in patients with cirrhosis and dilutional hyponatremia. In this study, 60 patients with cirrhosis and dilutional hyponatremia were randomly assigned to 100 or 200 mg/day of lixivaptan or placebo in a double-blind study. Treatment was given with fluid restriction (1,000 ml/day) until normalization of serum sodium or for 7 days. Normalization of serum sodium concentration was achieved in 27% and 50% of patients in the lixivaptan 100 mg/day and 200 mg/day groups, respectively, but in none of the patients in the placebo group (P < 0.05 and P < 0.001, respectively). Treatment with lixivaptan was associated with a significant reduction in urine osmolality and body weight. Thirst sensation increased significantly in the lixivaptan 200 mg group but not in the lixivaptan 100 mg or placebo group.

Satavaptan

Soupart et al. investigated the effect of satavaptan in patients with SIADH. In the first part of this multicenter trial, patients were randomly assigned to take either placebo or 25 mg or 50 mg daily of satavaptan for 5–23 days to obtain serum sodium within the range of 135–145 mmol/L. During the entire study, fluid intake was limited to 1500 ml/day. Baseline serum sodium levels were 125–127 mmol/L in the three treatment groups. Responders, defined as achieving normal serum sodium or increasing serum sodium level by at least 5 mmol/L from baseline over at least 24-hour period, were 79% (11 out of 14 patients) in the 25-mg group (P = 0.005 versus placebo), 83% (10 out of 12 patients) in the 50-mg group (P = 0.005 versus placebo) and 13% (1 out of 8 patients) in the placebo group. Urine osmolality decreased and free-water clearance increased with satavaptan. The long-term, open-label part of the study where 18 patients continued on satavaptan at doses 12.5 mg, 25 mg and 50 mg once daily for a period of 12 months showed effectiveness of satavaptan in maintaining normal serum sodium without drug escape and adverse effects. Hypernatremia developed in two patients during the double-blind period and five patients during the open-label period with satavaptan. No other drug-related serious events were reported.

CONCLUSION

Conventional treatment of hyponatremia is unpredictable and troublesome. Recent studies have shown that vaptans are quite efficacious in treating hyponatremia associated with SIADH, CHF and cirrhosis. Vaptans are well tolerated with only minor side effects including dry mouth, thirst and polyuria. Osmotic demyelination syndrome associated with rapid correction of hyponatremia has not been reported with the use of these agents till now. Presently, vaptans appear to be very effective in treating euvolemic and hypervolemic hyponatremia, but further studies on large number of patients are required to confirm the safety profile of these drugs.

REFERENCES