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Case Report

Loop diuretic-induced hyponatremia: a case report

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ABSTRACT

Hyponatremia is the most common encountered electrolyte abnormality where the serum sodium concentration is <136 mEq/L. The most common causes are either the concurrent illnesses or the medications. Diuretics top the list of drugs inducing hyponatremia and this occurs more frequent within 2 weeks of initiating therapy. Though thiazide diuretics are frequently the culprits of inducing hyponatremia, the role by/risk with loop diuretics cannot be ignored. Prompt diagnosis and management of hyponatremia needs a sound knowledge with which permanent neurologic sequelae and morbidity could be prevented. Here, we report a case of hyponatremia induced by loop diuretic and spironolactone combination, where the presenting complaints of the patient were only intractable nausea and altered taste. The patient was successfully managed with hypertonic saline and the vasopressin receptor antagonist, tolvaptan, which belongs to a new class of drugs called aquaretics.

Keywords: Diuretics-induced hyponatremia, Dysguesia, Vasopressin receptor antagonist, Hypertonic saline, Furosemide

INTRODUCTION

Hyponatremia is the electrolyte disorder most common encountered in clinical practice, with a reported incidence of 15-30%.[1] It should be differentiated from pseudo-hyponatremia, where increases in the non-aqueous components of plasma such as in hypertriglyceridemia or hyperproteinemia result in a spuriously low sodium concentration.[1]

Hyponatremic disorders are divided into euvolemic, hypovolemic, and hypervolemic.[2] Diuretic-induced hyponatremia (DIH) is one of the most common causes of hypovolemic hyponatremia and is associated with high urinary sodium.[3] Some studies have identified specific risk factors for the development of hyponatremia and these include: institutionalized elderly patients, low serum potassium concentration, low total body weight, and Indapamide use.[4,5]

The symptoms are primarily neurological and relate to the rapidity of fall of serum sodium.[6] Acute hyponatremia is defined as occurring within <48 hrs. There are usually no symptoms if serum sodium is 130-135 mmol/L. Nausea and malaise are seen if serum sodium falls to 125-130 mmol/L. Headaches, nausea, vomiting, muscle cramps, restlessness, disorientation, and depressed reflexes can be seen if serum sodium falls below 125 mmol/l.25. When severe hyponatremia evolves over a period of hours, seizures, coma, permanent brain damage, respiratory arrest, brain stem herniation, and death may occur.[7,8] In sharp contrast, patients with chronic hyponatremia are often asymptomatic irrespective of the degree of hyponatremia. Symptoms may only occur if there is acute exacerbation of hyponatremia, or if serum sodium falls below 110 mmol/L.[9]

The acute management of DIH is more determined by the presence or absence of neurologic symptoms than by the Na^+ level *per se*. Treatment consists of discontinuing diuretics,

regular diet (usually supplemented with K^+) restricting water, administration either isotonic saline or, if the hyponatremia is severe or symptomatic, hypertonic saline.[9] In asymptomatic or minimally symptomatic patients, stopping the offending diuretic and restricting water intake to <1 L/day is usually all that is needed. Normal saline is not needed unless correction of volume depletion is indicated. Increasing oral salt intake in combination with fluid restriction can increase serum Na^+ concentration.

CASE REPORT

A 57-year-old diabetic man who had undergone coronary artery bypass grafting (CABG) in a private hospital 1 month back came to the hospital with complaints of nausea, altered taste, and malaise for the past 1 week. He gives h/o intake of antiemetic for nausea 5 days back and there was no improvement of symptoms. The patient was admitted and evaluated.

Patient, a businessman by profession, a known case of diabetic on treatment with oral hypoglycemic drugs for the past 3 years was diagnosed with an old anterior wall infarct and had undergone CABG on May 20th 2015. Perioperative and post-operative period were uneventful, sutures were removed and he was discharged on 8th day. Prescription at discharge included anti-diabetic medicines, dual antiplateletes, angiotensin-converting-enzyme inhibitor, hypolipidemic drug, a fixed dose combination of furosemide with spironolactone and a multivitamin.

After 10 days of discharge, the patient gradually developed nausea and dislike toward solid food which worsened further. He was prescribed an antiemetic by a general practitioner but still complaints persisted. There is no h/o diarrhea/vomiting, abdominal pain, jaundice, edema, dysuria, fever/headaches, thyroid disorders, central nervous system disorders, breathlessness, post-operative pain, and smoking/alcohol intake. His investigation results showed hemoglobin -11.2%, casual plasma glucose - 132 mg/dl, blood urea, serum creatinine, lipid profile, liver function test, and urine routine analysis - normal.

Serum electrolytes revealed serum sodium - 124 mEq/L, serum potassium - 3.9 mEq/L, serum chloride - 92 mEq/L, urine sodium - 24 mmol/L. His thyroid function tests and ultrasound abdomen - normal. Echocardiography study: not suggestive of cardiac failure, no evidence of pulmonary hypertension. He was diagnosed as a case of DIH due to loop diuretic - furosemide as his serum sodium was low and his urine sodium was high and after all other probable causes for hyponatremia were ruled out.

DISCUSSION

Hyponatremia is an occasional but potentially fatal complication of diuretic therapy. Virtually all cases of severe DIH have been due to a thiazide-type diuretic.[10] In contrast, loop diuretics are implicated much less commonly.[11] This can be explained by the different nephronal sites of action of these two classes of diuretics. Thiazide diuretics inhibit NaCl reabsorption in the distal convoluted tubule, the main diluting site of the nephron. Thus, thiazide diuretics interfere with maximum dilution of urine because sodium (Na^+) excretion is increased along with diminished free water excretion 13, 14). On the other hand, loop diuretics inhibit NaCl reabsorption in the thick ascending limb of the loop of Henle. The reabsorption of NaCl without water in the medullary thick ascending limb is normally the primary step in the generation of the hypertonicity in the medullary interstitium, and loop diuretics mainly impair urinary concentration and limit water retention and development of hyponatremia.[12]

However, the present case was hyponatremia which was caused by loop diuretic furosemide further accentuated by spironolactone. Loop diuretic-induced fluid and electrolyte complication like hyponatremia often develops within the first 1-2 weeks of therapy if diuretic dose and dietary intake remain relatively constant.[8,13] In our case, symptoms of hyponatremia occurred after 10 days of using loop diuretic which is in line with the previous studies.

Even though hyponatremia can present with multivaried symptoms that can range from nausea, vomiting, dysguesia, malaise, headache, muscle cramps, restlessness, disorientation, depressed reflexes to seizures, coma, permanent brain damage, respiratory arrest and death, our patient presented only with nausea, sweet taste (dysguesia) and malaise for which he was prescribed an antiemetic ondansetron and despite the use of antiemetic therapy, the symptoms persisted. On presentation to our hospital with above-mentioned symptoms, electrolyte abnormality was suspected and the patient's blood was sent for serum electrolyte analysis where serum sodium was found to be 124 mEq/dL, which is classified under profound hyponatremia according to European guidelines for hyponatremia.[14,15]

The patient was treated by giving 100 ml of 3% Nacl solution as slow intravenous infusion per day for 3 days and tablet. Tolvaptan (*Resodim*®), a vasopressin receptor antagonist - an aquaretic. A dramatic improvement in patient's symptoms within 1 day was observed after giving afore mentioned treatment and the patient was discharged after ensuring that his electrolyte imbalance was corrected.

The aquaretics are a new line of agents which hold promise for future use in the treatment of hyponatremia. Vasopressin receptor antagonists block arginine vasopressin from binding to V2 receptors in the distal nephron and promote the excretion of electrolyte-free water.[16] In recent randomized trials, tolvaptan, an orally active V2 receptor antagonist, has been effective in raising serum sodium in patients with hyponatremia.[17]

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