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Symptomatic Hyponatremia in a Patient with Hepatorenal Syndrome Treated with Terlipressin

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Abstract

Terlipressin (vasopressin analogue) is considered most promising pharmacotherapy used for reversal of hepatorenal syndrome and esophageal variceal bleed. It occasionally results in hyponatremia, often complicated by serious central nervous system manifestation. We report here a case of a 60 years' old female known case of chronic liver disease decompensated who presented with acute kidney injury secondary to hepatorenal syndrome. Treatment was started with terlipressin loading dose followed by maintenance dose. She developed acute confusion however, there was no obvious brain pathology on computed tomography. Her baseline serum sodium (146.8mol/L) decreased to 111.5mmol/L after terlipressin was initiated. Terlipressin was withdrawn and patient responded to 3% hypertonic saline. Terlipressin-induced hyponatremia may be a rare complication and treating physicians should be aware of the possible complications arising during the management of hepatorenal syndrome.

Keywords: Terlipressin, Hyponatremia, Hepatorenal Syndrome, acute kidney injury, cirrhosis.

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Introduction

Acute kidney injury potentially complicates hepatorenal syndrome (HRS) in patients with chronic liver disease (CLD). Marked arteriolar vasodilation occurs in the splanchnic circulation resulting in reduced systemic vascular resistance and arterial hypotension.[1] Vasoconstrictive action of terlipressin (triglycyl-lysine vasopressin) along with albumin results in achievement of the effective circulatory volume. Terlipressin, has an agonistic action on vascular vasopressin receptors (arginine vasopressin type 1 receptors- V1); targeted at reversal of splanchnic arteriolar vasodilation. This can cause splanchnic vasoconstriction and result in a significant (around 30%) reduction of hepatic and portal venous blood flow in patients with portal hypertension. It is a time-honored treatment option for two serious complications in patients with cirrhosis; hepatorenal syndrome and variceal bleeding.[1,2] Additionally, Terlipressin activates renal vasopressin receptors (arginine vasopressin type 2 receptor-V2) located on basolateral aspect of renal epithelium. This action results in enhanced water permeability of renal tubules by 8-10 times and anti-diuresis. This leads to excessive water retention and potentially hyponatremia.[1]

We report the occurrence of symptomatic hyponatremia in a cirrhotic patient treated with terlipressin. This case report is presented to highlight the importance of plasma sodium level monitoring in patients being treated with terlipressin therapy.

Case Description

A 60-year-old woman, with decompensated CLD and portal hypertension for 3 years, had band ligation for esophageal variceal bleed three months prior to admission. Patient presented with abdominal pain, distension and constipation. Approximately six liters of therapeutic ascitic drainage was done few days ago. Physical examination revealed: blood pressure 105/74 mm of Hg, heart rate 86 beats/min, body temperature 36.3C and respiratory rate 16 breaths/mint. Patient was found to have gross ascites. She denied any recent history of diuretic use. Patient was given a controlled fluid challenge of 500 ml of isotonic saline. Pertinent laboratory data showed, hemoglobin 8.6 g/dL, platelet count 129,000/cmm, white blood cell count 8,400/cmm, serum sodium 146.8 mmol/L(normal range 135 – 145 mmol/L), serum chloride 98.2 mmol/L serum potassium 3.8 mmol/L, prothrombin time 11.3 seconds (international normalized ratio: 1.11), total bilirubin 1.2 mg/dL, albumin 4.04 g/dL, alanine aminotransferase 56 IU/L, aspartate aminotransferase 66IU/L, serum creatinine 6.67 mg/dL, and blood urea nitrogen 50 mg/dl. She had an admission diagnosis of Hepatorenal syndrome. Ultrasonography revealed features of coarse cirrhotic liver, ascites and bilateral normal renal echogenicity. As all physical parameters and laboratory variables were suggestive of hepatorenal syndrome, initial treatment included, prophylactic antibiotics, antacid (esomeprazole), parenteral nutrition supplement, and blood transfusion with red blood cells. In addition, terlipressin as a bolus dose of 2mg followed by 1mg every 8 hourly was started intravenously. Day next to initiation of terlipressin, her serum sodium was found to be 134.9 mmol/L. Foleys catheter was also inserted with no documented urine flow. Thus, hypertonic saline (3% sodium chloride) was administered to prevent the continuous decrease in serum sodium. On third day, patients' condition deteriorated. She developed confusion, altered mental state, and irritability, indicating progression of hepatic encephalopathy. Urgent brain CT scan was performed, but no organic lesion was revealed. Her serum sodium level on third day was also measured and found to be at a further lower level of 111.5 mmol/L and serum osmolality 242 mOsm/kg (normal range 285 – 295 mOsm/kg). Urine osmolality was not measured as patient was anuric. These observations suggested that the neurological features were due to severe hyponatremia in our patient. To reverse the neurological manifestations, a bolus dose of intravenous hypertonic (3%) saline was administered. Despite the reinforced injection of hypertonic saline, the serum sodium of the patient didn't improve. Considering terlipressin as the factor to induce symptomatic hyponatremia, terlipressin was immediately withheld and small boluses of hypertonic saline were given. Patient had persistent anuria with worsening renal functions. She could not be hemodialysed because of hemodynamic instability and unavailability of continuous renal replacement therapy. Norepinephrine was commenced at rate 3mcg/kg/min as continuous infusion. Due to multiorgan dysfunction patient unfortunately died on fifth day of admission.

Discussion

Terlipressin has a selective vasoconstrictive action on splanchnic versus vascular bed. This alleviates vasodilation of the splanchnic vascular bed and improves systemic arterial circulation to improve renal perfusion.[1,2]

Despite being a promising treatment for the variceal bleeding, the side effects of terlipressin, such as hyponatraemia, require careful attention.[3] The mechanism of action is to reduce portal venous inflow by causing splanchnic vasoconstriction through action on the V1 receptor.[4,5] However, terlipressin may concurrently activate the V2 receptor (located on renal tubules), which enhances aquaporin-2 incorporation onto the luminal membrane in the renal collecting duct. This results in enhanced water permeability of renal tubules by 8-10 times and anti-diuresis.[6] Therefore, free-water clearance and subsequently serum sodium concentration is significantly reduced. These events may lead to the development of hypervolemic hyponatremia and/or water intoxication.

Results of various studies have shown that the development of hyponatremia is not infrequent in patient' s being treated with terlipressin. In a multicenter controlled trial of 106 cirrhotic patients, 4 developed hyponatremia when treated with terlipressin while another trial by Feu et al. reported that hyponatremia occurred in 6% of patients.[7,8] Rapid recovery from hyponatremia after terlipressin withdrawal suggests its direct effect as reported in the literature.[9,10] Our patient however remained anuric and did not improve after Terlipressin withdrawal.

Hyponatremia is a frequently encountered electrolyte disorder in advanced cirrhotic patients secondary to non-osmotic release of antidiuretic hormone. This phenomenon can confuse the terlipressin-induced asymptomatic hyponatremia.[1] A careful evaluation of persistent hyponatremia is therefore needed in patients who are on terlipressin treatment.

Multiple studies have explained risk factors associated the development of hyponatremia in patients treated with terlipressin. In a recent case report of two patients, Meng Q at al showed that terlipressin-induced hyponatremia developed in patients with mild liver disease.[10] It was also observed that both Model for End-Stage Liver Disease (MELD) score and baseline serum sodium were related to the drop in serum sodium. Subjects with lower MELD scores and normal or near-normal baseline serum sodium concentration were found to be at the highest risk.[9] These findings are contrary to our case as our patient at presentation had a very high MELD score (22 points) and a normal serum sodium level (146mmol/L).

While treating patients at risk of development of hyponatremia, physicians should be aware of impending clinical sign of hyponatremic encephalopathy (such as headache, nausea, and vomiting), even if their baseline serum sodium level is above 130mmol/L. The gravest complication of hyponatremia, hyponatremic encephalopathy, can leave lasting neurological impairment and even death if not appropriately managed.[9] Other risk factors leading to severe neurological complications associated with hyponatremia are hypoxic state and premenopausal women.[11]

Conclusion:

Our observation highlights the importance of careful and frequent monitoring of plasma sodium level in CLD patients being treated with terlipressin. Clinicians managing CLD patients should be aware of the complication of life threatening hyponatremia with terlipressin treatment.

Conflict of Interest: none declared

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