Clinical Case Report

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Hypernatremia induced by low-dose Tolvaptan in a Patient with refractory heart failure

A case report

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Abstract

Rationale: Tolvaptan (TLV) is a selective vasopressin type 2 receptor antagonist, which has an active effect on patients with congestive heart failure especially combined with hyponatremia. Increasingly, evidence has demonstrated that low-dose tolvaptan can dramatically relieve patients' dyspnea and the dose would not cause severe electrolyte abnormalities. Even hypernatremia is a major adverse effect of tolvaptan, treatment with tolvaptan shows good security and is well-tolerated. Few cases have reported that patients who developed severe hypernatremia induced by low-dose Tolvaptan.

Patient concerns: A 68-year-old man was admitted to our hospital with dyspea and general fatigue. He was diagnosed with acute decompensated heart failure due to ischemic cardiomyopathy. In order to improve fluid retention and relieve his dyspnea, low-dose TLV (7.5 mg qd) was performed. After the 3-day treatment using TLV, we observed that he became delirious and his limbs shook uncontrollably. High serum sodium 173 mmol/L was noted compared to the results of the first examination (137 mmol/L). After intensive rescue, serum sodium was restored to normal (135 mol/L). Later, when the patient refused continuous renal replacement therapy (CRRT), we tried again to use a lower dose of TLV to improve diuretic resistance. Two days later, Serum sodium rose again (162 mmol/L).

Diagnoses: During the course of therapy, we did not strictly require the patient to control the fluid intake. No other medication could cause elevation of serum sodium. Therefore, we suspected a high sensitivity to the side effect of TLV.

Intervention: Stop the use of TLV and encourage the patient to drink plenty of water. Gastric tube was inserted orally to increase the intake of fresh water.

Outcomes: His serum sodium decreased gradually and his psychiatric symptom recovered. During this period, Overall condition of the patient was stable. After being discharged from the hospital, the patient eventually died of cardiac arrest due to critically ill heart failure.

Lessons: Hypernatremia is a severe side effect of TLV. For critical patients, TLV should be used at a low dose and electrolyte should be detected in time.

Abbreviations: AVP = vasopressin, CABG = coronary artery bypass grafting, CKD = chronic kidney disease, HF = heart failure, ICD = implantable cardioverter defibrillator, LVEF = left ventricular ejection fraction, mg = milligram, ml = milliliter, NT-ProBNP = Amino-terminal pro-B-type natriuretic peptide, TLV = tolvaptan, V2R = vasopressin type 2 receptor.

Keywords: diuretic resistance, heart failure, hypernatremia, side effect, tolvaptan

1. Introduction

Heart failure (HF) is a serious social and public health problem which draws great attention. Patients with refractory heart failure often face a difficult problem called diuretic resistance. Tolvaptan (TLV) is a selective vasopressin type 2 receptor antagonist, which shows an active effect on patients with congestive heart failure especially combined with hyponatremia.[1] Accumulating evidences have demonstrated that TLV in addition to standard therapy including Intravenous diuretics and nesiritide in patient with HF could improve patients' symptoms and quality of life in a short term without causing side effects on electrolytes, blood pressure or renal function.[1–3] Few case reports have mentioned the side effects of TLV. We herein present the case of a patient with HF who developed twice severe hypernatremia induced by low-dose TLV.

2. Case report

A 68-year-old man was admitted to our hospital with dyspea and general fatigue in July 2018. He was diagnosed with acute decompensated heart failure due to ischemic cardiomyopathy. The patient had a history of severe coronary heart disease and chronic kidney disease (CKD Stage II-III). During his last hospitalization in 2017, Coronary angiography showed severe

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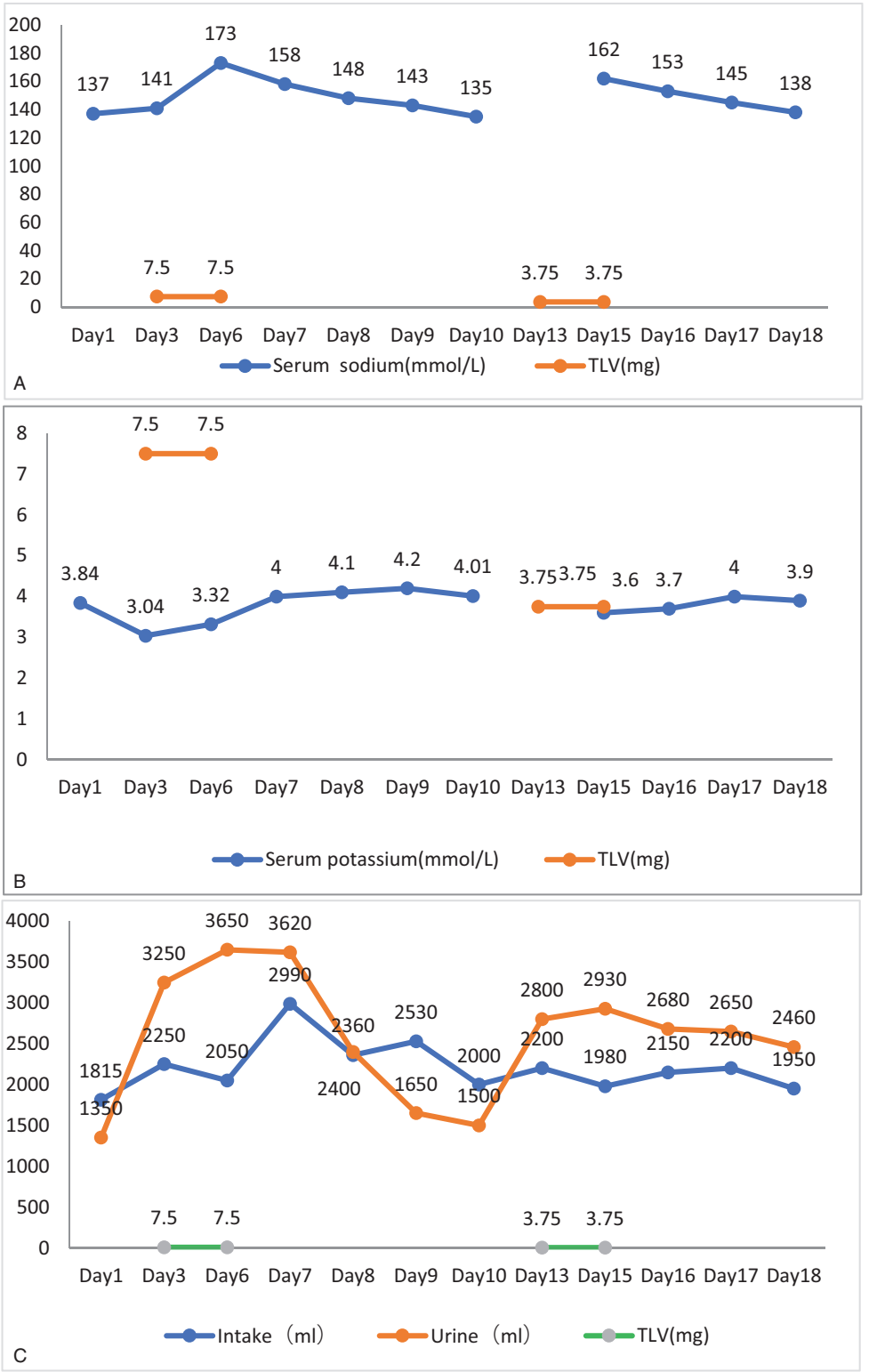

Figure 1. (A–C). Clinical course of the patient's condition.

triple vessel coronary artery disease, he refuse revascularization therapy. Holter revealed paroxysmal ventricular tachycardia and frequent ventricular premature beats, so he received implantable cardioverter defibrillator (ICD) treatment. Aspirin, atorvastatin, furosemide, spirolactone, perindopril and metoprolol were taken regularly at home. On the current admission, his blood pressure and heart rate were 135/82mmHg and 75beats/min respectively. A S3 and systolic murmur were identified alone with inspiratory moist rales in the bilateral lung fields with slight edema of both lower limbs. The first laboratory values were as follows: white

blood cells, 8.060/uL; hemoglobin, 14.6 g/dL; serum creatinine, 160 umol/L (estimated glomerular filtration rate 38 ml/min/1.73 m^2);blood urea nitrogen 12.0 mol/L, serum sodium, 137mmol/L; serum potassium, 3.84 mmol/L; amino-terminal pro-B-type natriuretic peptide (NT-proBNP), 25,000 pg/mL; cardiac troponin 0.11 ng/mL. Electrocardiogram revealed a sinus rhythm with a heart rate of 75 beats per minutes, ventricular premature beats, non-specific ST-T changes.

Chest X-ray showed cardiomegaly, left small pleural effusion and pulmonary congestion. Echocardiography demonstrated a sever left ventricular enlargement with decreased systolic function (left ventricular end-diastolic diameter, 65 mm; left ventricular ejection fraction, 28%), diffuse ventricular wall motion decrease, severe mitral regurgitation and moderate tricuspid regurgitation. The estimated pulmonary arterial pressure was 52 mmHg. The patient was diagnosed with acute decompensated heart failure caused by volume overload. In the initial treatment, intravenous loop diuretics and nesiritide were administrated as well as traditionally prescribed drugs. Because the patient was critically ill with heart failure and he was insensitive to intravenous diuretics, the patient's clinical symptoms did not improve significantly and his urine volume did not increase either. Therefore, diuretic resistance could be considered. In order to improve fluid retention and relieve his dyspnea, low-dose TLV (7.5 mg qd) was performed on day 3. The administration of TLV dramatically relieved dyspnea and increased urinary output. Cardiac rehabilitation was started gradually. Unfortunately after 3 days treatment of TLV, we observed that he became delirious and his limbs shook uncontrollably. High serum sodium 173 mmol/L was noted compared to the results of the first examination (137 mmol/L). Severe hypernatremia was diagnosed. Because no other medications were changed, we did not strictly require patient to control the fluid intake, and no other medication could cause elevation of serum sodium, we suspected a high sensitivity to the side effect of TLV. Hence, we stopped the use of TLV and encouraged patient to drink plenty of water, gastric tube was inserted orally to increase the intake of fresh water. After intensive rescue, serum sodium was restored to normal (135 mol/L) on day 10. The clinical data was as follows: white blood cells, 4, 010/uL; hemoglobin, 14.2 g/dL; serum creatinine, 104 umol/L (estimated glomerular filtration rate 62 ml/min/1.73 m^2); blood urea nitrogen 10.7 mmol/L, serum sodium, 135 mmol/L; serum potassium, 4.01 mmol/L; amino-terminal pro-B-type natriuretic peptide (NT-proBNP), 3280 pg/mL; Although the patient's laboratory results and clinical symptoms improved, he still needed intravenous diuretics to maintain liquid output. But he remained insensitive to them. Later, when the patient refused continuous renal replacement therapy (CRRT), we tried again to use a lower dose of TLV (3.75 mg qd) to improve diuretic resistance. 2 days later, Serum sodium rose again (162 mmol/L). We had confirmed that hypernatremia was caused by TLV. After the suspension of TLV, his serum sodium decreased to 138 mmol/L gradually, psychiatric symptom recovered. In order to maintain the patient's urine volume, We had to give the patient a larger dose of intravenous loop diuresis and nesiritide . During this period, the patient's overall condition was stable. He was discharged on the 21st day after admission. After hospital discharge, patient eventually died of cardiac arrest due to critically ill heart failure. Figure 1 (A–C) shows the clinical course of the patient during his hospitalization.

3. Discussion

As far as we know, diuretics play an important role in the treatment of acute decompensated HF. Traditional diuretics such as furosemide and so forth often cause renal insufficiency and electrolyte disorders.[4] 30% of patients had been observed with diuretic resistance in the Acute Decompensated Heart Failure Registry.[5] Tolvaptan (TLV) is an oral selective vasopressin type 2 receptor antagonist which exerts an aquaretic effect by blocking V2R in the renal collecting ducts resulting in the inhibition of water reabsorption without causing adverse effects on electrolytes, renal function and blood pressure.[1–3,6] Recently in China, TLV has been approved for volume control in patients with heart failure combined with diuretic resistance.

To the best of our knowledge, this is the first clinical case report to describe a patient with refractory HF that developed twice severe hypernatremia induced by low-dose TLV. Hyponatremia is common to be seen in hospitalized patients with HF, and it is also an independent predictor of prognosis.[7] Tolvaptan (TLV) provides a good choice for the treatment of hyponatremia, but sometimes it can cause the elevation of serum sodium. Hypernatremia has a rare adverse effect of TLV, and the mechanisms remain unclear. It may be the result of a combination of different mechanisms. Kinugawa et al proposed that predictive factors influencing the incidence of hypernatremia were higher serum sodium (≥142 mEq/L), starting dosage of tolvaptan at 15 mg/day and serum potassium <3.8 mEq/L.[8] In the post-marketing surveillance study and the EVEREST study,[1,8] during the tolvaptan treatment period, TLV did not significantly increase serum sodium levels in patients with normonatremia. The cause of hypernatremia in patient mentioned above seems to be as follows: first, the patient was older, who had low serum potassium on the current admission. Second, he has a history of chronic renal insufficiency as well as long-term HF, both of which connect and also influence each other closely; thus, it can lead to drug concentrations accumulating in the blood. Furthermore, the high sensitivity of individuals to TLV is also a factor that cannot be ignored. The above hypothesis needs further large studies to verify. How to use TLV effectively and avoid its serious side effects in time are still an urgent problem to be solved. In the clinical work, when treating refractory heart failure patients, TLV should be used at a low dose and electrolyte should be detected in time.

4. Consent for publication

Informed written consent was obtained from the patient for publication of this case report. The presented data are anonymized and risk of identification is minimal.

Author contributions

Conceptualization: GUI-Shuang Li.
Formal analysis: Tian Li.
Writing – original draft: Tian Li.
Writing – review & editing: GUI-Shuang Li.

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