Clinical Case Report

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A case report with shock induced by tolvaptan in an elderly patient with congestive heart failure

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Abstract

Rationale: Tolvaptan (TLV) is a new vasopressin type 2 receptor antagonist effective in patients with heart failure (HF). Accumulating evidences have revealed that treatment with TLV does not alter the blood pressure significantly.

Patient concerns: An 84-year-old man was diagnosed with acute exacerbation of chronic HF due to ischemic cardiomyopathy, arrhythmia, mitral and aortic regurgitation. Treatment with TLV increased the urine volume and improved the dyspnea. After 4 days use of TLV (3.75 mg QD, 7.5 mg QD, 7.5 mg QD, and 15 mg QD, respectively), decrease in blood pressure to less than 90/60 mmHg was observed continuously and the lowest blood pressure was 80/37 mmHg. He was apyretic and felt only thirsty. Central venous pressure was 12 cmH_2O.

Diagnoses: Because no other medications were changed and no signs of hypovolemic, septic, allergic, or cardiac shock were detected, we suspected an adverse reaction to TLV.

Intervention: Intravenous hydration was performed with 250 mL of normal saline.

Outcomes: His blood pressure increased gradually and the statue of hypotention lasted for 14 hours. The dose of TLV was decreased to 7.5 mg/d from the next day to discharge. During this period, his blood pressure was stable at about 125/60 mmHg.

Lessons: TLV has side effect of severe hypotension that is consistent with its physiological activity. The dose should be increased gradually to achieve the desired effect, while attention should be paid to potential drug interactions.

Abbreviations: AVP = vasopressin, BNP = B-type natriuretic peptide, BUN = blood urea nitrogen, CRT-D = cardiac resynchronization therapy and defibrillator, cTNI = cardiac troponin I, eGFR = estimated glomerular filter rate, Hct = hematocrit, HF = heart failure, LVEF = left ventricular ejection fraction, sPAP = systolic pulmonary arterial pressure, TLV = tolvaptan, V1aR = vasopressin type 1a receptor, V1bR = vasopressin type 1b receptor, V2R = vasopressin type 2 receptor.

Keywords: heart failure, shock, tolvaptan, vasopressin type 2 receptor antagonist

1. Introduction

Heart failure (HF) is a major public health problem. Tolvaptan (TLV), a new vasopressin type 2 receptor (V2R) antagonist, reduces congestion via the increased excretion of free water by blocking V2R at renal collecting ducts, subsequently correcting hyponatremia and improving the hemodynamics.[1,2] Several studies have demonstrated that treatment with TLV in addition to standard therapy including diuretics improves signs and symptoms of HF without causing serious adverse events.[1,2] Additionally, accumulating evidences have revealed that treatment with TLV does not alter the blood pressure significantly.[1,2] In contrast, few published case reports have described adverse events of TLV. We herein describe the case of an elderly patient with HF suffering from shock induced by TLV.

2. Patient information

An 88-year-old man with ischemic cardiomyopathy was admitted to our hospital for dyspnea, cough, expectoration, and edema in February 2016. He had once suffered from acute anteroseptal, inferior, and anterior myocardial infarction in 30, 16, and 4 years ago, respectively. He underwent coronary angiography in 2005, which showed triple vessel disease and did not undertake invasive treatment. Echocardiography in 2013 showed left atrial enlargement, left ventricular dilation, left ventricular segmental dyskinesia and dyssynchrony, moderate mitral regurgitation, mild aortic and tricuspid regurgitation, left ventricular ejection fraction (LVEF) 35%. Meanwhile, Holter showed polymorphous ventricular premature beat, paroxysmal ventricular tachycardia, atrial fibrillation, and first-degree atrioventricular block. So he received the treatment of cardiac resynchronization therapy and defibrillator (CRT-D) and had been treated with spirolactone, torasemide, indapamide, clopidogrel, asipirin, bisoprolol, nicorandil, isosorbide 5-mononitrate, amiodarone, rosuvastatin, carvedilol for chronic HF. Plasma B-type natriuretic peptide (BNP) fluctuated in 400 to 800 pg/mL during the last 3 years. He had also been diagnosed with essential hypertension and chronic kidney disease (Stage IV). On admission, his blood pressure and pulse rate were 170/90 mmHg and 90 beats/min, respectively. A third heart sound was identified, along with inspiratory moist rales in bilateral lung

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fields and bilateral lower limbs pitting edema. The initial laboratory data were as follows: white blood cells, 10,900/μL (78.1% neutrophilia); hemoglobin, 12.0 g/dL [hematocrit (Hct) 38%]; serum creatinine, 227.6 μmol/L [estimated glomerular filter rate (eGFR) 21.3 mL/min/1.73 m^2]; blood urea nitrogen (BUN), 14.73 mmol/L; BUN/creatinine ratio, 16.0; serum sodium, 128.8 mmol/L; serum potassium, 4.29 mmol/L; plasma BNP, 2401 pg/mL; and cardiac troponin I (cTNI), 0.15 ng/mL. Electrocardiography showed atrial fibrillation with a paced rhythm. A chest x-ray revealed cardiomegaly and multipatchy consolidations, which were mainly distributed in the right lower lung field. Transthoracic echocardiography demonstrated left ventricular dilatation and segmental dyskinesia with impaired left ventricular systolic function (end-diastolic diameter, 57 mm; end-systolic diameter, 47 mm; and LVEF, 38%), left atrial enlargement (dimension, 47 mm), severe mitral regurgitation, moderate aortic regurgitation and mild tricuspid regurgitation. The estimated systolic pulmonary arterial pressure (sPAP) was 44.5 mmHg. Additionally, the inferior vena cava was dilated. The patient was diagnosed with acute exacerbation of chronic HF caused by respiratory infection. Moxiflaxacin and digoxin were administrated and the usually prescribed drugs continued. Gradually, his condition improved. After 7 days of use, moxiflaxacin was stopped. His blood pressure and pulse rate were stable at about 130/65 mmHg and 65 beats/min, respectively. Serum BUN and creatinine gradually decreased to 11.91 mmol/L and 187.0 μmol/L (BUN/creatinine ratio, 15.8; eGFR 27.0 mL/min/1.73 m^2), respectively. But he intermittently needed continuous infusion of torasemide or furosemide (5–10 mg/h) in order to decrease volume load. So treatment with TLV started on day 38. The dose in the first 4 days (day 38, 39, 40, 41) was 3.75, 7.5, 7.5, and 15 mg, respectively. In the afternoon of day 41, decrease in blood pressure to less than 90/60 mmHg was observed continuously and the lowest was 80/37 mmHg. Meanwhile, his heart rate did not change significantly. He was apyretic and felt only thirsty. At that time, the volume of intake and urine was 850 and 200 mL, respectively.

3. Physical examination and diagnostic assessment

On physical examination, inspiratory moist rales in bilateral lung fields decreased, with lessened bilateral lower limbs edema. The clinical data were as follows: white blood cells, 7,200/μL (72.5% neutrophilia); hemoglobin, 11.9 g/dL (Hct 36%); serum creatinine, 237.4 μmol/L; BUN, 12.76 mmol/L; BUN/creatinine ratio, 13.3; serum sodium, 135.4 mmol/L; serum potassium, 3.6 mmol/L; BNP, 738 pg/mL; cTNI, 0.11 ng/mL; arterial blood gas (fraction of inspired oxygen 25%): pH 7.48, PaO_2 88 mmHg, $PaCO_2$ 36 mmHg, HCO_3- 26.8 mmol/L, lactate 0.8 mmol/L; fecal occult blood, negative. Electrocardiography showed no change compared with the previous one except for heart rate. Central venous pressure was 12 cmH_2O.

4. Therapeutic interventions

Because no other medications were changed and no signs of hypovolemic, septic, allergic, or cardiac shock were detected, we suspected an adverse reaction to TLV. Intravenous hydration was administrated with 250 mL of normal saline in the afternoon.

5. Follow-up and outcomes

His blood pressure increased gradually and the statue of hypotention lasted for 14 hours. The dose of TLV was therefore decreased to 7.5 mg/d from day 42 to day 46 when he was discharged. During this period, his blood pressure and pulse rate were stable at about 125/60 mmHg and 65 beats/min, respectively. Fig. 1 shows the clinical course of the patient.

Our case report was waived from Peking University First Hospital Ethical Board, based upon their policy to review all intervention and observational study except for a case report. The patient provided informed consent for the publication of his clinical data. The presented data are anonymized and risk of identification is minimal.

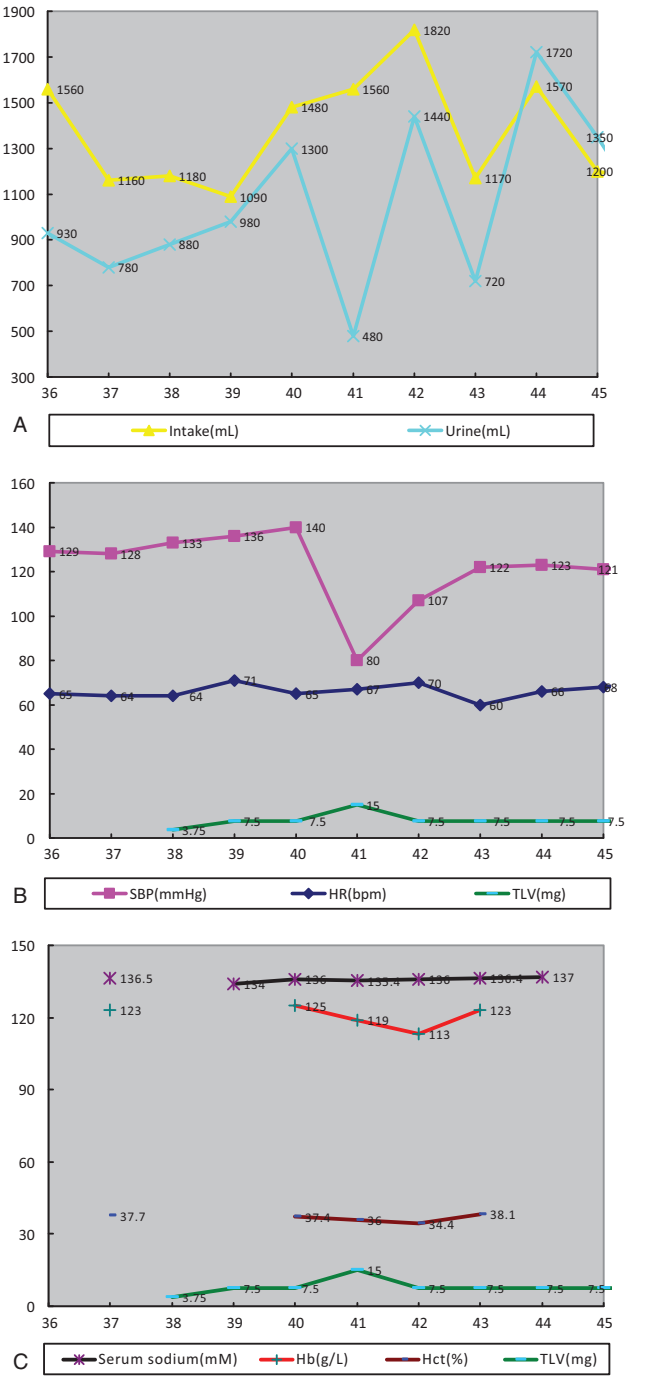

Figure 1. Clinical course of the patient's condition. Hb = hemoglobin, Hct = hematocrit, HR = heart rate, SBP = systolic blood pressure, TLV = tolvaptan. *Data obtained between day 36 and day 45.

6. Discussion

Vasopressin (AVP), a peptide hormone synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, is released in response to increases in plasma osmolarity or decreases in plasma volume in order to regulate body water content and excretion and blood pressure.[3] Once released into circulation, AVP acts on 3 distinct receptors: vasopressin type 1a receptor (V1aR), vasopressin type 1b receptor (V1bR), and V2R. The V1aRs are predominantly located in the heart, vascular smooth muscle cells and kidney, where stimulation is responsible for vascular constriction and possibly regulation of water reabsorption, respectively.[4] V1bRs are predominantly expressed in the pituitary.[4] While the V2Rs are predominantly expressed on the collecting ducts of renal tubules, where stimulation leads to the formation and insertion of aquaporin channels on the apical surface of collecting duct cells and allows an increase in water permeability and water retention.[5] Serum level of AVP is elevated in patients with HF and/or left ventricular (LV) dysfunction, and positively related to severity of HF.[6]

TLV, a selective vasopressin V2R antagonist, dose-dependently blocks AVP from binding to V2R and V1aR. The affinity with V2R is 30 times that with V1aR. TLV is primarily metabolized by cytochrome P450 3A4 in liver and its elimination half-life is 12 hours. TLV exerts aquaretic effects by blocking the V2R in the renal collecting ducts, which results in the inhibition of water reabsorption. When combined with standard therapy, TLV decreases the patient's body weight and edema, improves dyspnea, corrects hyponatremia in the setting of HF and appears to be well-tolerated without adversely affecting blood pressure, heart rate, the electrolyte levels or the renal function.[1,2]

To the best of our knowledge, this is the first report to describe a patient with HF who developed shock as a severe adverse reaction to TLV. The mechanisms of shock induced by TLV to this patient remain complex and it is likely a combined effect of different mechanisms. Firstly, hepatic metabolic dysfunction is a natural concomitant of old age. Furthermore, the patient was taking amiodarone—a CYP450 3A4 inhibitor. Both of the factors can lead to elevated serum TLV concentration. Although the affinity with V1aR is only one-thirtieth that with V2R, the effect of V1aR antagonism should not be ignored when serum TLV concentration is elevated, especially in the case of acute exacerbation of chronic HF where serum level of AVP is also elevated. And this may be one of the mechanisms of the shock. The above hypothesis was further supported by a gradual increase in blood pressure within subsequent 14 hours. Unfortunately, we could not provide data of serum TLV concentration. Secondly, the occurrence of severe hypotension and shock in this case on day 4 of using TLV may be partly due to relative hypovolemia in this fragile elderly patient with known stage IV renal failure. Although there had not been a significant change in terms of water balance than before and neither Hct nor BUN/creatinine ratio had suggested blood concentration, the possibility of relative hypovolemia still could not be excluded. Daily body weight is known to be more reliable than simply using the intake and output. Unfortunately, there were no complete data of body weight during TLV use because of the patient's fragility and bad compliance. The fact that the central venous pressure was 12 mmHg also does not exclude that possibility because the patient had some evidences of right ventricular dysfunction and tricuspid regurgitation.

This case report suggests TLV has side effect of severe hypotention that are consistent with its physiological activity. The dose should be increased gradually to achieve the desired effect, while attention should be paid to potential drug interactions.

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