Acute Renal Injury Induced by Hypersensitivity to Tolvaptan in an Elderly Patient with Congestive Heart Failure

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Abstract

Tolvaptan (TLV) is a new vasopressin type 2 receptor antagonist effective in patients with heart failure (HF). We herein describe the case of an 84-year-old woman who developed acute renal injury induced by hypersensitivity to TLV. The patient had received an implanted pacemaker and was diagnosed with exacerbation of chronic HF due to atrial fibrillation, mitral regurgitation, tricuspid regurgitation and left ventricular dyssynchrony. Treatment with tolvaptan increased the urine volume, improved the dyspnea and decreased the edema. However, the patient’s renal function and hyperkalemia worsened, and the blood eosinophil count increased without signs of dehydration or hypotension. Positive findings on a drug-induced lymphocyte stimulation test for TLV were consistent with this diagnosis.

Key words: diuretic, heart failure, vasopressin type 2 receptor antagonist

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Introduction

Heart failure (HF) is a major international public health problem. Tolvaptan (TLV) is a new vasopressin type 2 (V2) receptor antagonist effective in patients with decompensated HF. Tolvaptan reduces congestion via the increased excretion of free water by blocking V2 receptors at renal collecting ducts, subsequently correcting hyponatremia, an independent prognostic marker, and improving the hemodynamics (1-3). Several authors have suggested that the use of TLV in addition to standard therapy including diuretics improves many signs and symptoms of heart failure without causing serious adverse events in patients hospitalized with HF (1-3). Additionally, accumulating evidence has revealed that treatment with TLV does not alter the renal function and prevents worsening of the renal function more effectively than standard therapy in patients with HF (1-4). In contrast, few published case reports have described adverse events of TLV. We herein describe the case of an elderly patient with HF who developed acute renal injury induced by hypersensitivity to TLV.

Case Report

An 84-year-old woman with chronic atrial fibrillation and an implanted pacemaker was admitted to our hospital with dyspnea (New York Heart Association functional class III) and edema in November 2013. She had been treated with furosemide, azosemide, imidapril and warfarin for chronic HF. She had no previous history of allergies and had been diagnosed with renal dysfunction (serum creatinine, 1.5 mg/dL) of unclear etiology in 2011. On the current admission, she was 143 cm tall and weighed 54 kg, which was approximately 10 kg heavier than usual. Her blood pressure and pulse rate were 154/83 mmHg and 60 beats/min, respectively. Her temperature was 36.3°C, and she displayed no signs of infection. A third heart sound was identified, along with inspiratory moist rales in the bilateral lung fields, with jugular venous distension and systemic edema. Electrocardiography showed atrial fibrillation with a paced rhythm (Fig. 1A). The initial clinical data were as follows: white
blood cells, 6,510/μL (percentage of eosinophils to total white blood cells, 1.2%; eosinophil count, 78/μL); hemoglobin, 9.8 g/dL; serum creatinine, 1.5 mg/dL; blood urea nitrogen (BUN), 37.6 mg/dL; BUN/creatinine ratio, 25.1; serum sodium, 145 mEq/L; serum potassium, 3.5 mEq/L; plasma B-type natriuretic peptide (BNP), 1,089.5 pg/mL; and urine osmolality, 414 mOsm/L. A urinalysis showed slight proteinuria (±, 10-20 mg/dL) without occult blood, leukocytes or granular casts. A chest X-ray revealed cardiomegaly, pulmonary congestion and bilateral pleural effusion (Fig. 1B) despite the administration of loop diuretics (furosemide, 80 mg/day; azosemide, 15 mg/day). Transthoracic echocardiography demonstrated an impaired left ventricular (LV) systolic function with mild LV dilatation (LV end-diastolic diameter, 54 mm; LV end-systolic diameter, 42 mm; and LV ejection fraction, 40%), LV dyssynchrony due to right ventricular (RV) apical pacing, left atrial dilatation (left atrial dimension, 47 mm), moderate mitral regurgitation and severe tricuspid regurgitation. The estimated RV systolic pressure was high at 66 mmHg and RV dilatation was evident (RV end-diastolic diameter, 37 mm). Additionally, the inferior vena cava was also dilated.

The patient was diagnosed with exacerbation of chronic HF caused by volume overload. Fig. 2 shows the clinical course of the patient. The dose of azosemide, the standard prescribed drug, was stopped on day 1, while treatment with furosemide (80 mg/day) was continued. Additionally, TLV therapy (7.5 mg/day) was started. Although the administration of TLV increased the urine volume and slightly improved the patient’s dyspnea without causing hypotension, the serum sodium level increased to 152 mEq/L on day 3. Therefore, TLV was switched to intravenous carperitide (0.025 μg/kg/minute), which gradually decreased the urine volume. Since the serum sodium level improved to 141 mEq/L and the patient continued to weigh approximately 5 kg more than baseline, treatment with a lower dose (3.75 mg/day; 25% of the regular dose) of TLV was started on day 7. This strategy increased the patient’s urine volume and decreased her body weight without inducing hypernatremia. However, her renal function worsened, and hyperkalemia of 6.8 mEq/L as well as increased blood eosinophils were evident on day 11, whereas the urine volume remained constant at approximately 2,000 mL. Meanwhile, no decreases in the systolic blood pressure to less than 120 mmHg were observed during the TLV treatment. The patient’s heart rate did not change significantly, and the inferior vena cava remained dilated. Because no other medications were changed and no signs of intravascular volume loss were detected on echocardiography, we suspected an adverse reaction to TLV or carperitide. The dose of tolvaptan was therefore discontinued on day 12, and intravenous hydration was performed with 500 mL/day of half-normal saline.
The patient was encouraged to drink water, and a urinalysis revealed a small number of eosinophils without significant proteinuria and occult blood on day 16. The peak serum creatinine level was 2.9 mg/dL and the urinary β2-microglobulin increased to 440 μg/L on day 14. In addition, the BUN/creatinine ratio was 19.1. Hyponatremia, which can be induced by hydration, was observed at the same time. Although the eosinophil count remained elevated thereafter, the serum creatinine level, hyponatremia and hyperkalemia gradually improved, and the patient lost 7.5 kg compared with her weight observed on admission. Her symptoms were ultimately relieved, and the pleural effusion and cardiomegaly on chest X-ray improved (Fig. 1C). She was therefore discharged from the hospital on day 30 (BNP, 393.0 pg/mL). She demonstrated no further signs of worsening HF, and the blood eosinophil count decreased to 4.8% (225/μL) at four weeks after discharge. No leukocytes were detected on a repeat urinalysis. The discrepancy between the time of improvement in the serum creatinine level and that of the decrease in the eosinophil count in the blood appeared to be caused by the effects of hydration. The results of a drug-induced lymphocyte stimulation test (DLST) performed after discharge to identify the cause of the acute renal injury were positive for TLV, but not carperitide.

**Discussion**

To the best of our knowledge, this is the first report to describe a patient with HF who developed acute renal injury as a result of hypersensitivity to TLV. The oral V2 receptor antagonist TLV became available in Japan in December
For use in patients with HF accompanied by symptomatic congestion or hyponatremia (4, 5). Tolvaptan exerts aquaretic effects by blocking the V2 receptor 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 and 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 (1-6). Unlike furosemide, TLV appears to increase the renal flow in patients with HF (7). Additionally, TLV prevents worsening of the renal function more effectively than standard therapy (4) and reduces 60-day mortality rates in patients with renal dysfunction or severe systemic congestion (6). This evidence suggests that TLV favorably affects the renal function in patients with HF.

Many drugs used to treat HF may also influence the renal function in addition to diuretics (8). In the prospective randomized double-blind placebo-controlled Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, approximately 3% of patients randomized to receive TLV developed renal failure (1). However, the incidence of hypersensitivity to TLV in such patients remains unclear. Treatment with tolvaptan initially appeared to be effective in our patient, as the urine volume increased and the signs of HF improved. However, her renal function worsened and she developed hyperkalemia, although no signs of dehydration or hypotension were detected. The positive DLST findings indicated that hypersensitivity to TLV was likely involved in the underlying mechanism in this case, as well as the patient’s clinical course and the increased concentration of eosinophils in the blood. Therefore, hypersensitivity to TLV, in addition to classical diuretics, is an important factor with respect to worsening of the renal function during TLV treatment.

The authors state that they have no Conflict of Interest (COI).

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