Successful treatment with tolvaptan to control blood volume and hyponatremia in a chronic kidney disease patient

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Abstract We report a case of successful treatment with tolvaptan (15 mg/day) in a 73-year-old female patient with chronic kidney disease (CKD) stage 5 due to diabetic nephropathy and renal sclerosis for volume control and loop diuretic-induced hyponatremia. Her creatinine clearance has remained at 7–10 ml/min for the last 6 months. She was treated by dietary and drug therapy, namely, anti-hypertensives (nifedipine: 40 mg/day, olmesartan: 20 mg/day) and loop diuretics (azosemide: 40–120 mg/day), for CKD and concomitant diseases of hypertension and diabetic mellitus. She developed loop diuretic-induced hyponatremia (120 mmol/l) by increased sodium excretion, but the diuretic was required for the control of volume overload. Hence, azosemide was suspended and tolvaptan (15 mg/day) was administered. After tolvaptan treatment, the plasma sodium level gradually increased to a normal level (135–140 mmol/l) and volume overload was improved. Urine volume was maintained at about 1000 ml/day with low sodium excretion (<40 mmol/day) and increased free water clearance. These results suggest that tolvaptan may be effective for volume control and diuretic-induced hyponatremia in CKD patients.

Keywords Chronic kidney disease · Hyponatremia · Tolvaptan

Introduction

Volume overload is a critical problem in chronic kidney disease (CKD) patients because it is one of the main factors that lead to hypertension (HT) and cardiovascular disease (CVD) [1]. Since extracellular volume expansion and total body volume overload result from a failure of sodium and free water excretion in CKD [2], the use of loop and thiazide diuretics that increase sodium excretion is reasonable; however, these diuretics may cause hyponatremia and worse renal function [3]. Tolvaptan, an orally selective vasopressin V2 receptor antagonist reported to increase the excretion of excess fluids without increased sodium excretion, leads to improved hyponatremia in several diseases, such as heart failure, cirrhosis, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH), without adverse effects on renal function [4, 5]. However, the effects of tolvaptan in CKD patients remain to be estimated. We report successful treatment with tolvaptan for volume control and hyponatremia, which was caused by loop diuretics in a CKD stage 5 patient.

Case report

A 73-year-old female CKD patient was treated by dietary and drug therapy involving nifedipine (40 mg/day), olmesartan (20 mg/day), and azosemide (40 mg/day) in an outpatient department of our hospital. Her initial nephropathy was diabetic nephropathy and nephrosclerosis. Echocardiography showed normal cardiac function. Blood analysis showed that her plasma creatinine (Cr) level had increased to 2.5–3.0 mg/dl and her blood urea nitrogen (BUN) had increased to 30–50 mg/dl. Urinalysis showed proteinuria (0.5 g/day) without hematuria. CKD of this

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patient was categorized as stage 5 on the basis of the estimated glomerular filtration rate (eGFR) (9–11 ml/min/1.73 m²) and Cr clearance (7–10 ml/min) [6, 7]. Although her volume status and renal function were stable, and plasma electrolyte levels were maintained within normal ranges (sodium: 141 mmol/l, potassium: 4.0 mmol/l, chloride: 108 mmol/l), pleural effusion and leg edema developed in April 2011. Therefore, azosemide was increased to 80 mg/day to reduce the pleural effusion and edema. Although these symptoms were improved, her plasma sodium level decreased to 130 mmol/l by increased sodium excretion. After that, she showed a difficult pathologic condition, which involved hyponatremia (125–135 mmol/l) due to azosemide (40–80 mg/day), but azosemide was required for the control of volume overload. Although her renal function was kept stable, volume overload progressed regardless of the treatment with azosemide in the middle of September 2011. Then, azosemide was increased to 120 mg/day for the treatment of volume overload. The volume overload was improved; however, her plasma sodium level decreased to 120 mmol/l by increased sodium excretion. In accordance with this plasma sodium decrease, the patient complained of general fatigue and showed low physical activity. Therefore, azosemide use was suspended and the patient was admitted to our department to control volume status and hyponatremia at the end of September 2011.

Upon examination at admission, she had symptoms such as general fatigue and peripheral edema in her legs, but not nausea, seizure, hypotension, or a dry mouth. Her body weight was 47.6 kg and blood pressure (BP) was 163/58 (systolic/diastolic) mmHg. Blood analysis showed that her BUN level was 81 mg/dl, Cr level was 3.79 mg/dl, plasma sodium level was 126 mmol/l, plasma glucose level was 165 mg/dl, serum osmolality was 287 mOsm/l, and plasma antidiuretic hormone (ADH) level was 1.0 pg/ml (normal range 0.3–3.5 pg/ml). Her urine volume was 900 ml/day and urine protein was 0.62 g/day. Chest radiography showed a high cardiothoracic ratio (CTR: 56 %) and pleural effusion without pulmonary congestion (Fig. 1). Ultrasound cardiography demonstrated normal cardiac function (ejection fraction: 69 %). Her thyroid function was normal (thyroid-stimulating hormone: 0.45 μ IU/ml, triiodothyronine: 1.87 pg/ml, thyroxine: 1.1 pg/ml). Table 1 shows the other blood and urinalysis results upon admission. She was started on tolvaptan (15 mg/day following an initial dose of 7.5 mg/day on the first day). Upon tolvaptan treatment, the plasma sodium level gradually increased, with maintained urine volume of about 1000 ml/day and low sodium excretion (<40 mmol/day), as well as increased free water clearance (Fig. 1). Then, the plasma sodium level increased to 138 mmol/l, body weight decreased to 45.7 kg, BP decreased to

Fig. 1 Chest X-ray on admission

Table 1 Laboratory findings on admission

Blood analysis		Urinary analysis	
WBC	4700/mm ³	Volume	900 ml/day
RBC	281 $\times 10^4$ /mm ³	Protein	0.62 g/day
Hb	8.2 g/dl	Glucose	0.01 g/day
Ht	24.5 %	Osmolarity	243 mOsm
Plt	20.3 $\times 10^4$ /mm ³	UN	2.57 g/day
TP	7.3 g/dl	Cr	0.41 g/day
Alb	3.8 g/dl	Na	36 mmol/day
BUN	81 mg/dl	K	7.2 mmol/day
Cr	3.79 mg/dl	Cl	21.6 mmol/day
Na	126 mmol/l	Ccr	7.2 ml/min
K	4.4 mmol/l	pH	5.5
Cl	91 mmol/l	RBC	3–4/field
T-chol	132 mg/dl	WBC	14–15/field
HbA1c	5.6 %		
eGFR	9 ml/min/1.73m ²		
CRP	0.07 mg/dl		

WBC white blood cells, RBC red blood cells, Hb hemoglobin, Plt platelet, TP total protein; Alb albumin, BUN blood urea nitrogen, Cr creatinine, Na sodium, K potassium, Cl chloride, T-cho total cholesterol, HbA1c hemoglobin A1c, eGFR estimated glomerular filtration rate, CRP C-reactive protein, Ccr creatinine clearance

132/54 mmHg, CTR decreased to 50 %, and edema was improved without exacerbation of renal function on day 4 of tolvaptan treatment (Fig. 2). Her activity and general fatigue also improved. Since her body weight increased to 47.2 kg and CTR also increased to 53 % with low sodium excretion under tolvaptan treatment on day 9, azosemide (60 mg/day) was added (Fig. 2). Subsequently, the patient's body weight was maintained at about 46 kg, CTR

Fig. 2 Clinical course with tolvaptan treatment. *BW* body weight, *CTR* cardiothoracic ratio

was maintained at about 50 % without pleural effusion and edema, plasma sodium level was maintained at 135–145 mmol/l, and renal function was maintained at the basal level from before tolvaptan treatment (BUN 70–80 mg/dl, Cr 3.5–3.9 mg/dl), with moderate sodium excretion (80–100 mmol/day).

Discussion

We have demonstrated the therapeutic effects of tolvaptan for volume control and hyponatremia, which was caused by loop diuretics in a CKD stage 5 patient. CKD can lead to sodium retention with subsequent volume overload [2]. Therefore, loop and thiazide diuretics are the first-line drugs to control volume overload in CKD because they increase water excretion in accordance with sodium excretion. However, CKD occasionally shows a difficult pathologic condition, that is, hyponatremia by traditional diuretics; nonetheless, such diuretics are required for the treatment of volume overload. Volume overload is the main factor of HT that leads to CVD [1]. Hyponatremia is also reported to be associated with increased morbidity and mortality in various diseases, including CKD [8–11]. Therefore, both volume overload and hyponatremia should be corrected in CKD. Chow et al. [12] reported that more than 200 CKD patients whose eGFR was 47 ± 22 ml/min exhibited thiazide-induced hyponatremia over a period of

6 years. This result suggested that diuretic-induced hyponatremia in CKD patients is not rare.

Tolvaptan is an orally selective vasopressin V2 receptor antagonist reported to increase the excretion of excess fluids without an increase of sodium excretion [13]. Tolvaptan inhibits the binding of arginine vasopressin to the V2 receptors on the collecting ducts of the kidneys, resulting in aquaresis, the excretion of water without electrolyte loss [13]. Although several studies reported that tolvaptan significantly increased the plasma sodium level in chronic heart failure, cirrhosis, and SIADH, its effects in CKD remain to be elucidated because the patients with a serum creatinine concentration of more than 3.5 mg/dl were excluded in those previous studies [4, 5]. In this study, tolvaptan was effective in a CKD stage 5 patient to increase the plasma sodium concentration and control blood volume. Although we could not completely rule out the contribution of uremia to the symptoms of this patient, such as general fatigue and low physical activity, we determined that hyponatremia mainly contributed to these symptoms because the renal function did not decrease compared with that observed 6 months previously. Indeed, after tolvaptan treatment, these symptoms were improved in accordance with the improvement of the plasma potassium level. The plasma ADH level did not increase in this patient, suggesting that hyponatremia was mainly due to increased sodium excretion by diuretics in this case. Renal replacement therapies, such as hemodialysis and the extracorporeal ultrafiltration method, while paying attention to the risk of a decrease of residual renal function, could be alternative therapies to manage volume overload and diuretic-induced hyponatremia in this patient [14].

The most frequently observed adverse effects of tolvaptan are thirst and dry mouth [4, 15]. Myelinolysis, which is caused by the rapid correction of hyponatremia, is a serious side effect of tolvaptan [15]. In addition, Irazabal et al. [16] reported that tolvaptan significantly reduced the GFR during a one-week treatment, with an increase of uric acid in autosomal dominant polycystic kidney disease (ADPKD) patients. Higashihara et al. [17] reported that tolvaptan caused various adverse effects such as thirst, pollakuria, nasopharyngitis, hypertension, and dizziness in the long term (>3 years) in ADPKD patients. Therefore, careful and periodical blood and urine analysis will be required in this patient, although no side effects, including decreased Cr clearance and increased plasma uric acid, were observed during the short-term tolvaptan treatment.

Since this is only one case report suggesting the beneficial effects of tolvaptan for volume control and diuretic-induced hyponatremia in CKD stage 5, further studies will be required in order to evaluate the treatment and adverse effects of tolvaptan in CKD patients.

In conclusion, tolvaptan may be effective for volume control and hyponatremia caused by loop diuretics in CKD stage 5 patients.

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Conflict of interest All authors have declared that they have no competing interests.

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