Successful Conversion From Thiazide to Tolvaptan in a Patient With Stage D Heart Failure and Chronic Kidney Disease Before Heart Transplantation

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SUMMARY

Chronic kidney disease (CKD) is often complicated with advanced heart failure because of not only renal congestion and decreased renal perfusion but also prolonged use of diuretics at higher doses, which sometimes results in hyponatremia. Preoperative CKD is known to be associated with poor prognosis after heart transplantation (HTx). We experienced a stage D heart failure patient with CKD and hyponatremia who was switched from trichlormethiazide to tolvaptan. His hyponatremia was normalized, and his renal function was improved after conversion to tolvaptan. In patients with stage D heart failure, it may be useful to administer tolvaptan with a concomitant reduction in the dose of diuretics in order to preserve renal function and avoid hyponatremia before HTx. (*Int Heart J* 2013; 54: 48-50)

Key words: Hyponatremia, Diuretics, Renal dysfunction

Chronic kidney disease (CKD) and hypervolemic hyponatremia are often complicated with advanced heart failure, and are not only attributable to renal congestion and reduced renal perfusion but also to extended use of diuretics at higher doses.¹⁻⁵ Heart transplantation (HTx) is the comprehensive solution for patients with stage D heart failure refractory to optimal medical therapy thus far,⁶ but it is well known that preoperative CKD results in a poor prognosis after HTx.⁷ It is especially important to preserve preoperative renal function since postoperative immunosuppressive therapy cannot help some kinds of renal impairment.⁸ We experienced a stage D heart failure patient with CKD who was administered tolvaptan (TLV) and a vasopressin type 2 (V2) receptor antagonist, along with discontinuation of trichlormethiazide. His hyponatremia normalized and his renal function improved. Furthermore, his renal function remained within an acceptable range after HTx under immunosuppressive therapy including a calcineurin inhibitor.

CASE REPORT

The patient was a 53-year-old male with ischemic cardiomyopathy (Figure 1, Table) who had received coronary artery bypass surgery in March 2010. His heart failure worsened even after the bypass surgery, and he eventually became dependent on intravenous infusion of inotropes regardless of maximum

medical therapy including carvedilol, enalapril, spironolactone, trichlormethiazide, and furosemide in August 2010. He was transferred to our hospital as a possible candidate for HTx in September 2010. His laboratory data on admission showed 137 mEq/L of serum sodium, 1.9 mg/dL of serum total bilirubin, 1.2 mg/dL of serum creatinine, and 636 pg/mL of plasma B-type natriuretic peptide. Transthoracic echocardiography indicated an ejection fraction of 28% and left ventricular diastolic diameter of 67 mm. A hemodynamic study performed in December 2010 demonstrated that mean right atrial pressure was 2 mmHg, mean pulmonary capillary wedge pressure was 21 mmHg, and the cardiac index was 2.2 L/minute/m² under continuous infusion of inotropes. He was then listed in February 2011 as a recipient of HTx. In the meantime, his serum creatinine increased to 1.4 mg/dL and his serum sodium concentration decreased below 130 mEq/L probably because of incremental dose of diuretics. However, we could not decrease the dose of diuretics for fear of inducing fatal decompensation.

In November 2011, he received furosemide at 60 mg/day, torasemide at 4 mg/day, and trichlormethiazide at 4 mg/day as diuretics. We then considered whether his renal dysfunction and hyponatremia could be reversed by reduction of any of the above diuretics. We chose to discontinue trichlormethiazide since 4 mg/day of the thiazide might be excessive in combination with loop diuretics. However, we were concerned that the condition of his heart failure did not allow us simple cessation of trichlormethiazide, so we decided to introduce TLV at 3.75

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Figure 1. Clinical course of the case before and after the administration of tolvaptan. BW indicates body weight; sCr, serum creatinine; sNa, serum sodium; UV, urine volume; HTx, heart transplantation; and CyA, cyclosporin.

Figure 2. Time course of urine osmolality during the administration of tolvaptan. U-OSM indicates urine osmolality. *data were obtained just before the administration of tolvaptan (baseline urine osmolality). †Data were obtained 4 hours after the administration of tolvaptan.

Table. Laboratory, Urine, and Echocardiographic Parameters

	1 month before the administra- tion of TLV	1 month after the administra- tion of TLV	2 months after HTx
<i>Laboratory parameters</i>			
White blood cell count, × 10 ³ /μL	7300	5600	7400
Hemoglobin, g/dL	11.2	10.7	11.1
Platelets, ×10 ³ /μL	30.3	22.9	24.3
Serum sodium, mEq/L	128	136	138
Serum total bilirubin, mg/dL	0.7	0.9	0.7
Serum AST, IU/L	18	15	8
Serum ALT, IU/L	16	12	14
Serum BUN, mg/dL	30.3	19.5	38.8
Serum creatinine, mg/dL	1.44	1.17	1.19
Serum BNP, pg/mL	432	330	100
Serum osmolality, mOsm/L	262	279	284
<i>Echocardiographic parameters</i>			
Ejection fraction, %	13	21	65
LVDd, mm	62	66	48

TLV indicates tolvaptan; HTx, heart transplantation; AST, aspartate amino transferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; and LVDd, left ventricular diastolic diameter.

mg/day and then titrated up to 7.5 mg/day in place of the thiazide. After switching to TLV, serum creatinine decreased below 1.2 mg/dL and serum sodium normalized up to 135 mEq/L. The urine osmolality responses after the administration of TLV were typical for a responder of this V2 receptor antagonist (Figure 2). He underwent HTx in July 2012, and his serum creatinine remained below 1.5 mg/dL regardless of cyclosporine treatment.

DISCUSSION

Elevated venous pressure, low cardiac output, neurohormonal activation including the renin-angiotensin system con-

tribute to renal dysfunction in patients with advanced heart failure.¹⁾ Hypervolemic hyponatremia results from water retention by way of increases in arginine vasopressin (AVP) levels and/or decreases in glomerular filtration.²⁾ Especially in patients with stage D heart failure, almost all patients are dependent on high doses of diuretics for long periods, which facilitate both renal dysfunction and hyponatremia. Diuretic-induced renal dysfunction is due to decreased glomerular filtration by secondary stimulation of renin/angiotensin and norepinephrine secretion. On the other hand, hyponatremia caused by diuretics is attributable to increased excretion of sodium in urine and inappropriate AVP secretion against low or normal serum osmolality.³⁻⁵⁾ Consistently, our patient had a measurable concentration of AVP (2.7 pg/mL) despite low serum osmolality (262 mOsm/L) when he had hyponatremia just before conversion to TLV. Moreover, several investigators demonstrated that there was a dose-dependent association between diuretic use and mortality.^{9,10)} Even if we acknowledge such drawbacks of higher doses of diuretics, we could not avoid using considerable amounts of diuretics because he easily fell into a decompensated state without them.

Recently, TLV has been demonstrated to be advantageous in the correction of hyponatremia,^{11,12)} stabilization of hemodynamic state,¹³⁾ and amelioration of congestion without a worsening of renal function.¹⁴⁾ Administration of TLV along with discontinuation of trichlormethiazide successfully reversed his hyponatremia and renal dysfunction. We decided to discontinue trichlormethiazide because of its relatively weak diuretic effect and worsening effect on renal function compared with loop diuretics.⁵⁾ Several authors including us have reported that ventricular assist device (VAD) implantation can reverse end-organ dysfunction significantly.^{15,16)} Currently, approximately 90% of Japanese recipients require VAD support for bridge to HTx,⁷⁾ mainly because of the progressive decline in end-organ function that occurs in most patients with end-stage heart failure. Fortunately, he could be managed without VAD implantation until HTx, but preserving renal function was especially important considering the long waiting period before HTx. Moreover, treatment with a calcineurin inhibitor after HTx of-

ten worsens renal function by decreasing the glomerular filtration ratio due to constriction of afferent glomerular arterioles of the kidneys,⁸⁾ but thanks to the preoperative recovery of renal function by conversion of diuretics, his serum creatinine level remained below 1.5 mg/dL after HTx.

We administered TLV at first at 3.75 mg/day because of concern of a decrease of blood pressure due to large-scale diuresis. Urine osmolality was sufficiently higher than serum osmolality before TLV treatment, and significantly decreased at 4 hours after the administration of TLV, which implied effective excretion of free water.¹³⁾ The continuous decrease in urine osmolality after the titration of TLV up to 7.5 mg/day indicated that TLV was sufficiently effective. Patients with more advanced CKD may not respond to TLV because of their inability to concentrate and dilute urine, which can be partly explained by an attenuated V2 receptor/aquaporin-2 system in the collecting duct,¹⁷⁾ though this has not been definitively determined. As we have previously reported,¹⁸⁾ responders to TLV are normally associated with significant decreases in urine osmolality after TLV treatment (ie, > 26% decrease of urine osmolality at 4-6 hours) from considerably high baseline levels (ie, > 352 mOsm/L), which represent preserved function of the collecting duct including abilities to both concentrate and dilute urine. We were able to confirm in this case the criteria for TLV responders we proposed previously.

In conclusion, though no previous report has demonstrated an advantage in the conversion of conventional diuretics to TLV thus far, the present findings strongly suggest that TLV may be useful for improving hyponatremia and CKD, which may also lead to successful HTx in such cases waiting for long periods before HTx.

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