A Case With Recovery of Response to Tolvaptan Associated With Remission of Acute Kidney Injury and Increased Urine Osmolality

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SUMMARY

Tolvaptan (TLV), a vasopressin type 2 receptor antagonist, has been demonstrated to be effective in patients with decompensated heart failure (HF) refractory to incremental doses of diuretics, but the responsiveness has not always been predictable. We have recently proposed that urine osmolality (U-OSM) is a valuable parameter for the prediction of responses to TLV because U-OSM reflects the activity of the collecting ducts, where TLV plays its unique role. Acute kidney injury (AKI) is often associated with severe tubular dysfunction, including the collecting ducts, and in such cases a response to TLV may not be expected. We here experienced a patient with HF and AKI in whom TLV was not effective during AKI. We also observed recovery of responsiveness to TLV along with remission of AKI as well as increased U-OSM later on. We believe that this is the first report on the reversibility of the TLV response in relation to U-OSM. (Int Heart J 2013; 54: 115-118)

Key words: Renal dysfunction, Vasopressin, Heart failure, Rejection

Patients with advanced heart failure (HF) are often refractory to incremental doses of diuretics because of enhanced tubular water reabsorption, mainly by vasopressin inappropriately released in response to low-normal serum osmolality, and eventually encounter severe congestion and hypervolemic hyponatremia. Tolvaptan (TLV), a vasopressin type 2 (V2) receptor antagonist, has been demonstrated in recent studies to be efficacious in the correction of congestion and hyponatremia. However, the response to TLV is not always predictable. We recently demonstrated that no significant decrease in urine osmolality (U-OSM) at a certain period after the administration of TLV from relatively lower baseline U-OSM represents unresponsiveness to TLV. This phenomenon is explained by the inability to concentrate and dilute urine predominantly in the collecting duct. In the midst of acute exacerbation of renal insufficiency, ie, acute kidney injury (AKI), we sometimes observe that TLV is not effective for diuresis. In such cases, acute tubular necrosis might be attributable to unresponsiveness to TLV. Here, we report a patient with HF who was a nonresponder to TLV during AKI, but eventually turned into a responder to TLV after the recovery of renal function.

CASE REPORT

The patient was a 16-year-old female who underwent heart transplantation in the United States when she was 4 years old. She had been treated with tacrolimus and azathioprine. Her last endomyocardial biopsy at 2 years before the present admission showed no evidence of rejection and a left ventricular ejection fraction (LVEF) of 70% by transthoracic echocardiography. Unscheduled hospitalization became necessary because she complained of dyspnea and orthopnea due to acute decompensated HF.

Clinical data on her admission showed serum creatinine of 1.07 mg/dL, plasma B-type natriuretic peptide (BNP) of 1646 pg/mL, LVEF of 25% by transthoracic echocardiography, and U-OSM of 804 mOsm/L (Table). Endomyocardial biopsy showed diffuse infiltration of lymphocytes and myocardial injury with deposit of complements, which indicated both cellular and antibody-mediated rejection.

First stage (during AKI, Figure 1): After her admission, methylprednisolone pulse therapy and immunoglobulin administration were given for rejection, but her renal function worsened and urine volume (UV) reduced gradually along with progression of HF regardless of maximum medical therapy consisting of incremental doses of intravenous infusion of inotropes, furosemide, and carperitide. Fractional excretion of fil-

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Fractional excreted sodium (FENa) was 5.17% and fractional excretion of filtered urea nitrogen (FEUN) was 38.7% at day 10. Significant numbers of hyaline and epithelial casts were observed in the whole field of the urine. Serum neutrophil gelatinase-associated lipocalin (NGAL) was 365 ng/mL. As we could not manage her congestion, we started TLV at 3.75 mg/day at day 10 and titrated up to 15 mg/day in 3 days. Baseline U-OSM just before the administration of TLV was 330 mOsm/L, and U-OSM had barely decreased at 4 hours after the administration of TLV (Table). Daily UV further reduced to nearly anuria within a few days and then she was diagnosed as AKI (AKI Network stage 3).13 She eventually became dependent on continuous hemodiafiltration (CHDF).

Second stage (post AKI, Figure 2): Her congestion worsened...
around day 70 with recurrence of cellular rejection, albeit modest regardless of the administration and titration of enalapril, spironolactone, and furosemide. Elevation of BNP levels was observed (~900 pg/mL), though LVEF was preserved. We restarted 3.75 mg/day of TLV after methylprednisolone pulse therapy once. No hyaline and epithelial casts were observed in urine at this time, and the serum NGAL level was undetectable (ie, < 60 ng/mL). UV increased along with significant reduction in U-OSM at 4 hours after the administration of TLV (237 mOsm/L) from higher baseline U-OSM (432 mOsm/L). After TLV treatment, her congestion was successfully treated with decreased levels of plasma BNP and body weight. No electrolyte imbalance, including sodium and potassium, was observed throughout the clinical course.

**DISCUSSION**

When we administered TLV in the first stage during AKI, U-OSM did not decrease significantly at 4 hours after TLV treatment, which implied ineffective excretion of free water.19 As we recently reported, responders to TLV are normally associated with significant decreases in U-OSM after TLV treatment (ie, > 26% of U-OSM at 4-6 hours) from considerably higher baseline levels (ie, > 352 mOsm/L), which represent preserved function of renal tubules, including both abilities in concentrating and diluting urine.20 Conversely, patients with advanced chronic kidney disease (CKD) are often nonresponders to TLV because of their inability to control U-OSM, which can be partly explained by physiological adaptation to increased solute load on remaining nephrons and decreased osmotic gradient toward inner medulla.12,18 She was clearly a nonresponder to TLV during AKI as predicted by U-OSM criteria.

In the first stage during AKI, her renal dysfunction worsened gradually regardless of maximal medical therapy. High FE\( _{\text{Na}} \) and FE\( _{\text{UN}} \) (> 1.0% and > 35%, respectively) and significant numbers of hyaline and epithelial casts in urine, all indicated that renal parenchymal disease was a dominant cause of her oliguria.12,16 The elevated serum NGAL level (> 150 ng/mL) also indicated direct epithelial damage in the renal tubules.17 Antigen-antibody complex induced by antibody-mediated rejection as well as long-term usage of tacrolimus may have contributed to her renal parenchymal disease.18,19 Decreased renal perfusion due to lower cardiac output might have contributed to her renal dysfunction, but low renal perfusion does not usually associate with severe renal parenchymal disease by itself.

We previously reported that patients with a reduced estimated glomerular filtration rate (eGFR) tended to not respond to TLV treatment, while at the same time a certain number of patients with stage IV CKD (< 30 mL/minute/1.73m\(^2\) of eGFR) were good responders to TLV.22 This phenomenon means that reduced GFR is not always associated with tubular dysfunction in chronic phase. Collecting duct function is known to be relatively preserved until the end-stage of CKD because of its resistance to ischemia owing to low oxygen consumption.23 However, this scenario is not applicable to AKI like in our patient. In fact, her U-OSM decreased below 350 mOsm/L on July 29, and at the same time her eGFR was also below 30 mL/minute/1.73m\(^2\). Therefore, unresponsiveness to TLV during AKI may be explained by physiological adaptation of renal tubules to the low number of active nephrons, and also a result from direct injury to renal tubules, including collecting ducts.

After CHDF treatment for approximately 1 month, her renal function recovered and U-OSM became higher than serum osmolality. In the second stage (post AKI), we again administered TLV on the hypothesis that she turned into a responder. As we suspected, her U-OSM decreased at 4 hours after TLV administration, and her congestion was successfully treated with decreases in body weight and BNP level. We believe that this is the first report on the reversibility of responses to TLV in the same patient. We emphasize that monitoring of U-OSM is useful to find the best timing to administer TLV, especially in patients with AKI, because responsiveness to TLV can be recovered along with tubular function.

**REFERENCES**

15. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the frac-


