Urine Osmolality-Guided Tolvaptan Therapy in Decompensated Heart Failure

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Heart failure (HF) is a clinical state characterized in part by intravascular and extracellular volume excess. Loop diuretics have a high natriuretic potency by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle and remain the first-line treatment for ameliorating symptoms associated with volume overload. Thiocarbamide diuretics inhibit sodium transport in the distal tubule and can block the compensatory increase of sodium reabsorption in the response to loop diuretics, which results in a much greater natriuretic effect than when a loop diuretic is given alone. However, natriuretic therapy alone is not sufficient to control fluid retention from both the aspect of neurohormonal regulation and of renal sodium-water handling in patients with advanced HF. The natriuretic-induced sodium loss activates not only the renin-angiotensin-aldosterone (RAA) and sympathetic nervous systems, but also stimulates non-osmotic release of arginine vasopressin (AVP). Increased AVP secretion activates the V2 receptor and induces water reabsorption via cyclic adenosine monophosphate (cAMP)-stimulated aquaporin (AQPs)-2 translocation into the apical plasma membrane of the principal cells in the distal nephron. Notably, activation of the V2 receptor also increases the expression of the Na-K-2Cl transporter in the thick ascending limb of the loop of Henle and stimulates the epithelial Na channel (ENaC) in the distal nephron via cAMP, which enhances sodium reabsorption. Consequently, non-osmotic stimulation of AVP secretion results in sodium-water reabsorption and plays a contributory role in refractoriness to loop diuretics. Therefore, V2 receptor antagonism may both induce aquaresis and restore the response to natriuretics, and consequently optimize renal sodium-water handling.

Tolvaptan (TLV), a selective V2 receptor antagonist, has recently been available for patients with HF and symptomatic congestion. Recent clinical studies in Japan have demonstrated that short-term TLV treatment increased urine volume (UV), decreased body weight, and improved signs of fluid overload in patients with HF and excess fluid retention despite receiving loop and/or thiazide diuretics. However, the effects of TLV on UV may vary widely, depending on several factors, including age, baseline medications, renal function, and the severity of HF. Therefore, TLV may ineffective in a certain number of patients with HF. Although the pathophysiological mechanisms governing non-response to TLV are complex and multifactorial, in this issue of the Journal, Imamura et al identify predictors of TLV efficacy, and used them to successfully stratify responders/non-responders to TLV among 61 consecutive in-hospital patients with decompenated HF. In their study, a responder/non-responder to TLV was defined as having any increase/decrease in UV during the 24 h after TLV treatment on the first day. Using receiver-operating characteristic analysis, they found that 2 criteria, consisting of baseline urine osmolality (U-OSM) >352 mOsm/L (C1), and per cent decrease in U-OSM ≥26% at 4–6 h after TLV administration (C2), had much better predictability for responders than the estimated glomerular filtration rate (eGFR). They suggest that the kidneys of non-responders may no longer have diluting ability and may also barely retain concentrating ability. Interestingly, their data showed that certain patients with preserved eGFR had none or minimal response to TLV. These results may indicate that a disability of AVP/AQP-2 system in the collecting duct is at least partially independent of glomerular function.

Renal excretion of water and major electrolytes exhibits a significant circadian rhythm. U-OSM normally varies between 100 and 1,200 mOsm/kg and is usually highest during the night because of an increase in the plasma AVP level. Therefore, U-OSM measurement early in the morning may be optimal for testing the concentrating ability of the kidneys. However, the 24-h periodicity of U-OSM can be altered in patients with HF and renal dysfunction, and is also influenced by multiple factors, including the amount and timing of fluid ingestion and medications. Therefore, patients with preserved urinary concentrating ability, but impaired urinary circadian rhythm, may have a negative C1 result when tested only in the early morning. Optimal timing of U-OSM measurements for predicting the efficacy of TLV warrants further investigation in a larger population to reduce false-negative results. Imamura et al also measured U-OSM at 4–6 h after TLV treatment, and a per cent decrease of U-OSM ≥26% had high sensitivity and specificity for predicting UV increase, suggesting its great utility as a surrogate marker for the effectiveness of TLV on free water excretion. Although initial blocking effects of TLV on the AVP/AQP-2 system are expected 4–6 h after drug administration, they may be delayed by intestinal congestion, which prevents proper absorption of TLV in patients with much...
more severe hemodynamic status. Therefore, certain patients with negative C2 results may have a late, positive response to TLV treatment.

Although the authors emphasize that the non-invasively estimated cardiac index, right ventricular systolic pressure, and pulmonary wedge pressure values obtained from echocardiography were not significantly different between responders/non-responders, further work is needed to elucidate whether inability to concentrate and dilute urine owe fully to intrinsic renal injury or are partially secondary to the underfilling and/or hypoxemia associated with a severely deteriorated hemodynamic status. The authors did not observe dose-dependent responses to TLV in terms of UV increase, which strongly indicates that the dose-response relationship for TLV varies widely among individual patients. As over-diuresis will activate the RAA and sympathetic nervous systems, accelerate renal dysfunction, and induce hypernatremia, further research is needed to identify patient-specific factors that will influence the choice of optimal individualized TLV dosing, not only to minimize the false-negative results but also to avoid over-diuresis.

Imamura et al also demonstrate that urine sodium concentration did not change after the administration of TLV in responders, suggesting net sodium excretion increased while urine urea nitrogen significantly decreased, together with lowered U-OSM. These results may indicate that non-osmotic stimulation of AVP activates not only free water but also sodium reabsorption, and may play a contributory role in the refractoriness to natriuretics in a complex mechanism involved in aggravation of renal congestion and acceleration of ENaC-mediated sodium reabsorption in the distal nephron through the V2 receptor and downstream cAMP-mediated pathways.

In summary, Imamura et al have identified predictors of TLV efficacy, and successfully stratified responders/non-responders to TLV by measuring U-OSM and found that their 2 new criteria had great predictability for responders. Their methods, results, and cutoff points as presented are worth referencing in future studies. These new criteria will assist physicians in deciding whether TLV treatment should or should not be continued in patients with HF.

References