Adding High-Dose Spironolactone to Tolvaptan Improves Acute Decompensated Heart Failure Due to Obstructive Hypertrophic Cardiomyopathy and Aortic Stenosis: A Case Report

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Conflict of interest: None declared

Patient: Female, 86
Final Diagnosis: Advanced heart failure
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Medications for advanced heart failure
Specialty: Cardiology

Objective: Unusual setting of medical care
Background: In the setting of acute decompensated heart failure (ADHF), tolvaptan, a selective V₂ receptor antagonist, did not alter plasma renin activity or angiotensin II level, but significantly increased plasma aldosterone by the activation of V₁a receptor, suggesting that a high-dose mineralocorticoid receptor antagonist (MRA) combined with a V₂ receptor antagonist might be of interest, especially in ADHF patients. However, in the setting of ADHF, the short-term and long-term efficacy of a high-dose MRA combined with tolvaptan remains unclear.

Case Report: An 86-year-old woman with a history of chronic HF with a preserved ejection fraction due to obstructive hypertrophic cardiomyopathy and severe aortic stenosis was transferred to our hospital complaining of persistent dyspnea (New York Heart Association class IV). She did not respond to standard therapy with tolvaptan (15.0 mg/day). However, the present case demonstrated that adding high-dose spironolactone (100 mg/day) to low-dose tolvaptan (15.0 mg/day) is safe and well tolerated, resulting in an increase in urine output and improvement of the symptoms or signs of ADHF in a patient who was refractory to loop diuretics and tolvaptan.

Conclusions: The short- and long-term efficacy of high-dose spironolactone combined with low-dose tolvaptan may be associated with an attenuation of the aldosterone level, which is increased through V₁a activation by vasopressin during tolvaptan administration.

MeSH Keywords: Aortic Stenosis, Subvalvular • Cardiomyopathy, Hypertrophic • Heart Failure • Receptors, Vasopressin • Spironolactone

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Background
Tolvaptan is a selective V2 receptor antagonist that can relieve the signs and symptoms of heart failure (HF) without altering blood pressure or affecting renal function [1–4]. Recently, it was reported that vasopressin induces aldosterone release from adrenal gland cells through activation of the V1a receptor, and that vasopressin promotes an increase in renin-angiotensin-aldosterone system (RAAS) activity by modulating macula densa cells via the V1a receptor [5,6]. It was also reported that tolvaptan did not alter plasma renin activity or the angiotensin II level, but significantly increased plasma aldosterone [7]. This means that the reactive increase in vasopressin in HF patients receiving tolvaptan is associated with elevation of aldosterone level, suggesting that a high-dose mineralocorticoid receptor antagonist (MRA) combined with a V2 receptor antagonist might be of interest, especially in acute decompensated heart failure (ADHF) patients [8]. However, the short- and long-term efficacy of a high-dose spironolactone combined with tolvaptan remains unclear in the setting of ADHF. We report the case of an elderly female patient who had ADHF with a preserved EF due to obstructive HCM and severe AS. When high-dose spironolactone (100 mg/day) was added to low-dose tolvaptan (15.0 mg/day), this patient showed good short- and long-term response.

Case Report
An 86-year-old woman with a history of chronic HF due to obstructive HCM and AS was transferred to our hospital complaining of persistent dyspnea (New York Heart Association class IV). She was on multiple medications for management of chronic HF, including torasemide (8 mg/day), spironolactone (25 mg/day), metoprolol (120 mg/day), losartan (50 mg/day), and disopyramide (300 mg/day). On admission, her blood pressure was 98/74 mmHg and her heart rate was 54 beats/min. Echocardiography revealed a left ventricular (LV) ejection fraction of 68% with LV wall thickness of 20 mm, a peak left ventricular outflow tract (LVOT) gradient of 144 mmHg at rest due to systolic anterior motion of the mitral valve, and moderate to severe mitral regurgitation. In addition, echocardiography demonstrated severe AS (peak aortic valve velocity of 5.7 m/s and mean aortic valve gradient of 48 mmHg). As shown in Figure 1, we could distinguish between obstructive HCM and severe AS (i.e., dynamic vs. fixed obstruction) by the shape of the continuous-wave Doppler velocity curve [9]. A chest radiograph revealed moderate pulmonary congestion and bilateral pleural effusions (Figure 2). Based on these findings, she was diagnosed as having ADHF with a preserved EF due to obstructive HCM and severe AS. Laboratory tests showed that blood urea nitrogen was 33.2 mg/dl, serum creatinine was 0.60 mg/dl, serum sodium was 142 mEq/l, serum potassium was 4.2 mEq/l, and B-type natriuretic peptide (BNP) was 5857 pg/ml. Oxygen saturation was below 90% on room air. She was not considered to be a candidate for implantation of a permanent pacemaker, septal ablation with ethanol, or surgical therapy because of her advanced age and insufficient motivation. Therefore, intravenous administration of furosemide (40 mg/day) was added from day 1 after hospital admission, and low-dose tolvaptan (7.5 mg/day) was added from day 4 to keep the serum sodium concentration within normal limits.
the normal range. Over a 4-day period after admission, a total urine output of 1000 to 1200 ml/day was transiently maintained with coadministration of furosemide (bolus infusion of 40 to 60 mg/day), spironolactone (50 mg/day), and low-dose tolvaptan (7.5 mg/day), but the patient’s orthopnea and oxygen saturation showed little improvement. Accordingly, dose escalation was performed for both tolvaptan (increased from 7.5 to 15.0 mg/day) and furosemide (bolus infusion was increased from 60 to 80 mg/day), but there was no significant improvement of ADHF by hospital day 19. In addition, her urine output gradually decreased despite up-titration of tolvaptan to 15.0 mg/day. However, soon after up-titration of spironolactone (from 50 to 100 mg/day) was added to tolvaptan at 15.0 mg/day, total urine output exceeded 1500 ml/day and was maintained at this level during hospitalization, despite tapering and discontinuation of furosemide. Her dyspnea was also markedly alleviated and she improved from New York Heart Association class IV to class III. Chest radiographs obtained on hospital day 25 showed very little pulmonary congestion or residual pleural effusion. Since discharge from hospital, she has remained on the same medications and has been followed up at our outpatient department for 18 months without adverse changes of serum electrolytes or readmission for exacerbation of HF (Figure 3).

Discussion

It is well documented in the literature that a selective V$_2$ receptor antagonist results in sustained body weight loss along with an early decrease in pulmonary capillary wedge pressure without RAAS activation [10,11]. However, there is a reactive increase in vasopressin that results in activation of the unprotected V$_1a$ receptor in the myocardium and vascular wall during tolvaptan administration [1,8,12]. It has also been shown that V$_1a$ receptor deficiency leads to hyporeninemic hypoaldosteronism, while V$_1a$ receptor stimulation promotes aldosterone production by the adrenal gland [13]. Taken together, these reports suggest that the reactive increase in vasopressin in HF patients receiving tolvaptan is associated with elevation
of the aldosterone level [12–14]. Recently, Pitt et al. reported that combining a V$_{2}$ receptor antagonist with high-dose MRA might be useful for ADHF [8]. However, little information has been available regarding the efficacy of high-dose spironolactone combined with tolvaptan in ADHF patients. The present elderly patient had ADHF with a preserved EF due to both obstructive HCM and severe AS. Her baseline serum sodium concentration (142 mEq/l) was at the high end of the normal range. She did not respond to standard therapy with low-dose tolvaptan (15.0 mg/day). It is noteworthy that up-titration of tolvaptan from 7.5 to 15.0 mg/day resulted in a decrease in the urine output. We hypothesized that the addition of high-dose spironolactone (≥100 mg/day) to tolvaptan would attenuate an increase in aldosterone levels by V$_{1a}$ activation by vasopressin, which was displaced during tolvaptan administration, and that this combination therapy could lead to an increase in urine output. As expected, up-titration of spironolactone from 50 to 100 mg/day combined with tolvaptan at 15.0 mg/day achieved rapid and significant improvement of ADHF. No adverse effects of this combination therapy were noted during the short- and long-term phases of treatment. It was reported that the elevation of aldosterone in HF patients receiving tolvaptan might require addition of high-dose MRA therapy to block the MR and thus achieve diuresis [8]. Accordingly, the combination of a selective V$_{2}$ receptor antagonist with a high-dose MRA could achieve an increase in urine output along with a decrease in plasma volume [8]. However, we had no data regarding plasma aldosterone concentrations in the present case, suggesting that further study will be necessary to examine potential associations among spironolactone doses, plasma aldosterone concentrations, and outcomes in ADHF patients. However, with regard to the safety of high MRA doses in HF patients, it was reported that the diuretic resistance of loop diuretics may be reversed with high-dose MRA, and the resultant increased urinary potassium losses may also protect against any clinically relevant hyperkalemia in HF patients who receive a high-dose spironolactone [15]. Indeed, a small study reported that loop diuretic-resistant patients who were on angiotensin-converting enzyme inhibitor treatment for cardiac failure demonstrated an important natriuresis with 100 mg/day spironolactone without any clinically important rise in plasma potassium concentration [16]. However, in elderly HF patients with high-dose loop diuretic resistance, the safety of use of high-dose MRA has not been fully evaluated.17 Accordingly, further studies evaluating the safety and efficacy of high-dose spironolactone associated with overcoming high-dose loop diuretic resistance are necessary for elderly HF patients.

Conclusions

The present case demonstrates that adding high-dose spironolactone to low-dose tolvaptan is safe and well tolerated, resulting in an increase in urine output and improvement of the symptoms or signs of ADHF in a patient who was refractory to high-dose loop diuretics. The short- and long-term efficacy of high-dose spironolactone combined with low-dose tolvaptan may be associated with an attenuation of the aldosterone level, which is increased through V$_{1a}$ activation by...
vasopressin during tolvaptan administration. Thus, the present case suggests that an addition of high-dose spironolactone to tolvaptan is beneficial for advanced HF patients refractory to standard medical therapy for ADHF. However, a prospective study is required to examine the efficacy and safety of combining of tolvaptan with high-dose spironolactone for the treatment of ADHF.

Conflict of interest

None.

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