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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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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 V_2 receptor antagonist, did not alter plasma renin activity or angiotensin II level, but significantly increased plasma aldosterone by the activation of V_{1a} receptor, suggesting that a high-dose mineralocorticoid receptor antagonist (MRA) combined with a V_2 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 V_{1a} 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 V_2 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 V_{1a} receptor, and that vasopressin promotes an increase in renin-angiotensin-aldosterone system (RAAS) activity by modulating macula densa cells via the V_{1a} 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 V_2 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 hypertrophic cardiomyopathy (HCM) and severe aortic stenosis (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 hypertrophy (maximum 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

Figure 1. Continuous-wave Doppler echocardiography on admission. (A) Continuous-wave Doppler of the LVOT jet with a characteristic late peaking velocity curve, showing measurement of the peak pressure gradient (132 mmHg). (B) Continuous-wave Doppler of the AS jet with a characteristic early peaking velocity curve, showing measurement of the maximum velocity (5.7 m/s) and tracing of the velocity curve to calculate the mean aortic valve gradient (48 mmHg). Note the different shapes of the 2 velocity curves, with the late-peaking maximum velocity curve indicating dynamic obstruction (A) and the early-peaking curve indicating fixed obstruction (B). LVOT – left ventricular outflow tract; AS – aortic stenosis.

Figure 2. Clinical course in hospital. The up-titration or down-titration of medications (furosemide, torasemide, spironolactone, and tolvaptan) while in hospital is shown, along with the daily urine output, serum sodium, and potassium concentration, and chest radiographs. IV – intravenous infusion.

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,⁶ 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

Figure 3. Chest radiographs, laboratory data, body weight, and NYHA functional class. **(A)** Before discharge from hospital. **(B)** At 18 months after discharge. BNP – B-type natriuretic peptide; NYHA – New York Heart Association.

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 P[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.

References:

1. Lee CR, Watkins ML, Patterson JH et al: Vasopressin: A new target for the treatment of heart failure. *Am Heart J*, 2003; 146: 9–18
2. Gheorghiade M, Gattis WA, O'Connor CM et al: Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA*, 2004; 291: 1963–71
3. Konstam MA, Gheorghiade M, Burnett JC Jr. et al: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA*, 2007; 297: 1319–31
4. Udelson JE, Orlandi C, Ouyang J et al: Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: An international, multicenter, randomized, placebo-controlled trial. *J Am Coll Cardiol*, 2008; 52: 1540–45
5. Birumachi J, Hiroyama M, Fujiwara Y et al: Impaired arginine-vasopressin-induced aldosterone release from adrenal gland cells in mice lacking the vasopressin V1A receptor. *Eur J Pharmacol*, 2007; 566: 226–30
6. Aoyagi T, Izumi Y, Hiroyama M et al: Vasopressin regulates the renin-angiotensin-aldosterone system via V1a receptors in macula densa cells. *Am J Physiol Renal Physiol*, 2008; 295: F100–7
7. Costello-Boerrigter LC, Boerrigter G et al: Renal and anti-aldosterone actions of vasopressin-2 receptor antagonism and B-type natriuretic peptide in experimental heart failure. *Circ Heart Fail*, 2010; 3: 412–19
8. Pitt B, Gheorghiade M: Vasopressin V1 receptor-mediated aldosterone production as a result of selective V2 receptor antagonism: A potential explanation for the failure of tolvaptan to reduce cardiovascular outcomes in the EVEREST trial. *Eur J Heart Fail*, 2011; 13: 1261–63
9. Baumgartner H, Hung J, Bermejo J et al: EAE/ASE. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*, 2009; 10: 1–25
10. Udelson JE, Orlandi C, Ouyang J et al: Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: An international, multicenter, randomized, placebo-controlled trial. *J Am Coll Cardiol*, 2008; 52: 1540–45
11. Veeraveedu PT: Effects of V2-receptor antagonist tolvaptan and the loop diuretic furosemide in rats with heart failure. *Biochem Pharmacol*, 2008; 75: 1322–30
12. Konstam MA, Udelson JE: Hyponatraemia and vasopressin in heart failure: Markers or mediators? *Eur J Heart Fail*, 2011; 13: 242–44
13. Izumi Y, Hori K, Nakayama Y et al: Aldosterone requires vasopressin V1a receptors on intercalated cells to mediate acid-base homeostasis. *J Am Soc Nephrol*, 2011; 22: 673–80
14. Gheorghiade M, Pang PS, Ambrosy AP et al: A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are re-hospitalized within 90 days: Analysis from the EVEREST trial. *Heart Fail Rev*, 2012; 17: 485–509
15. Schrier RW, Masoumi A, Elhassan E: Aldosterone: Role in edematous disorders, hypertension, chronic renal failure, and metabolic syndrome. *Clin J Am Soc Nephrol*, 2010; 5: 1132–40
16. van Vliet AA, Donker AJ, Nauta JJ, Verheugt FW: Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. *Am J Cardiol*, 1993; 71: 21A–28A
17. Albaghdadi M, Gheorghiade M, Pitt B: Mineralocorticoid receptor antagonism: Therapeutic potential in acute heart failure syndromes. *Eur Heart J*, 2011; 32: 2626–33