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Original Article

Short-Term Effects of Tolvaptan in Patients with Severe Chronic Kidney Disease and Heart Failure with Fluid Overload

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Background: In patients with severe chronic kidney disease (CKD), congestive heart failure (CHF), diuretic resistance, and hyponatremia represent treatment impediments. Tolvaptan, a diuretic with a new mechanism of action, selectively binds to vasopressin V2 receptor and inhibits reabsorption of water. Its effects on heart failure (HF) have been proven, but its benefit to patients with CKD has not been confirmed. In this study, we examined the effects of tolvaptan on patients with severe CKD and HF.
Materials and methods: We analyzed patients with stage 5 CKD and CHF that was resistant to existing diuretics. Urine volume, urine osmolality, body weight, sodium (Na) level, and B-type natriuretic peptide (BNP) were the main effective endpoints and analyzed laboratory data.
Results: There was no clinically significant hypernatremia. However, free water clearance did show an increasing tendency. Urine volume increased significantly ($P = 0.026$), while body weight ($P < 0.01$) and BNP ($P = 0.006$) decreased significantly. There were no significant changes in serum creatinine (Cr) level or adverse events.
Conclusion: Tolvaptan has a diuretic effect in patients with severe CKD and CHF but does not cause clinically significant hypernatremia or adverse effects on renal function. Adding tolvaptan to conventional loop diuretic can enhance diuresis.

Keywords: Tolvaptan, Chronic kidney disease, Diuretic, Congestive heart failure, Worsening renal function

Introduction

Chronic kidney disease (CKD) is a strong and independent risk factor for cardiovascular disease (CVD) and the prevalence of CVD directly correlates with the severity of CKD [1]. Heart failure (HF) is highly prevalent in patients with CKD and end-stage renal disease (ESRD) and is strongly associated with mortality in these patients. HF is the leading cardiovascular (CV) complication in CKD patients and its prevalence increases with declining kidney function [2]. B-type natriuretic peptide (BNP) is a biomarker of CVD that is common in patients with CKD [3]. In

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patients with HF, BNP secretion from ventricular myocytes increases in relation to the degree of dysfunction, which substantiates its use in the diagnosis, screening, prognosis, and monitoring of patients with CV conditions [4]. Natriuretic peptide-"guided" care of HF patients is based on a low BNP target value [5]. However, the treatment of congestive heart failure (CHF) in this population is largely unclear. HF treatment is defined as any formal means taken to improve the symptoms of HF and/or the heart structure and functional abnormalities. Control of fluid overload, the use of beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and optimization of dialysis appear to be the most important methods for treating HF in CKD and ESRD patients [6]. In CKD patients, maintaining salt and water balance and improving blood pressure control are key strategies for reducing both the risk and the manifestations of HF [7]. Diuretic therapy often requires higher doses than in HF patients with normal kidney function [8]. Loop diuretics should be used as first-line agents in patients with glomerular filtration rate (GFR) <30 mL/min/1.73m^2 but resistance to loop diuretics is common in patients with advanced CKD, due to glomerular loss, tubular resistance from chronic diuretic use, secondary hyperaldosteronism, reduced intestinal drug absorption, and inadequate salt and water intake [9, 10].

Tolvaptan binds selectively to the V2 receptor (1 of 3 vasopressin receptors: V1a, V1b, and V2), disturbs the movement of aquaporin 2 into the luminal side of cortical collecting duct cells through activation of cAMP, and inhibits reabsorption of water. It uses a new mechanism of action for producing water diuresis [11, 12] that differs from conventional diuretics [13]. The short-term effects of tolvaptan for treating HF have been investigated in the ACTIVE in CHF [14] and EVEREST [15, 16] trials. Volume depletion by diuresis leads to a decrease in renal blood flow in patients with severe renal dysfunction. Thus, renal function may worsen. In previous studies, renal blood flow and GFR were not reduced by tolvaptan [17, 18].

Tolvaptan is an approved drug for HF that causes aquaresis. Its clinical efficacy for patients with severe kidney disease and decompensated HF has yet to be elucidated. There are few reports on the effects of tolvaptan on severe kidney disease with CHF [19, 20]. The aim of this study is to determine the short-term hemodynamic effects of tolvaptan in this population, including diuretic response, systemic hemodynamic characteristics, and renal function.

Materials and methods

Subjects

This is a retrospective observational study of usual practice, with no planned protocol. Tolvaptan is indicated for adults with clinically significant euvolemic or hypervolemic hyponatremia, including patients with HF, cirrhosis, and secretion of inadequate antidiuretic hormone. Six patients presented with hyponatremia, CKD stage 5, and CHF with fluid overload. Patients were required to meet at least 1 of the following criteria for enrollment: estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2; serum sodium (Na) <134 mmol/l; and administration of intravenous furosemide of at least 40 mg. Subjects were also required to have signs of extracellular volume expansion, defined as ≧ 2 of the following: jugular venous distention, pitting edema (≧ 1+), ascites, pulmonary congestion on chest x-ray, and/or pulmonary rales. Exclusion criteria included supine systolic blood pressure < 90 mm Hg; dialysis; serum Na >144 mEq/l; refractory, end-stage HF; and acute coronary syndrome or percutaneous coronary intervention within 30 days of the study.

We explained the possible side effects of tolvaptan to all patients and obtained their consent. Patients with stage 5 CKD and CHF who were admitted to our hospital for fluid overload and dyspnea were enrolled. Tolvaptan dose was 15 mg/day. The treatment target value for serum Na concentration was 144 mEq/l. If the serum Na concentration increased to ≧145 mEq/l, tolvaptan was discontinued. Urine volume and serum BNP were assumed to be the main effective endpoints. We evaluated free water clearance, body weight, serum

osmolality, serum creatinine (Cr) level, Na level, and adverse events. In addition, we compared laboratory examination data including acid-base status of blood gases (PH, HCO3, PCO2), potassium (K), calcium (Ca), and phosphate (P) before and after the administration of tolvaptan. The Ethics Committee of Chung Shan Medical University Hospital approved this study (CS2-19040). Supported by Chung Shan Medical University Hospital, Taichung, Taiwan, No. CSH-2017-A-015.

Statistical analysis

The value of each measurement is expressed as mean ± standard deviation (SD). We conducted one-way analysis of variance (ANOVA) by considering data multiplicity over time and used Tukey's multiple comparison test for the subsequent post hoc test. Paired t test was applied to comparisons of variables. We considered $P<0.05$ to be statistically significant.

Results

Tables 1 and 2 provide a summary of patient backgrounds. The study group consisted of 6 women with a mean age of 76 ± 13.8 years, a mean serum Cr level of 5.8 ± 1.8 mg/dl, a mean eGFR of 8.3 ± 3, and a mean Na level of 131 ± 2 mmol/l at the time of admission. All 6 patients were reported to be of cardiac functional class V, according to New York Heart Association (NYHA) criteria. Mean BNP was 2308.3 ± 459.7. Primary diseases included diabetic nephropathy (DN, n=3) and nephrosclerosis (n=3). Patients were administered intravenous furosemide (180mg/day) but not digitalis. The dose of tolvaptan remained constant after the 3rd day.

Urine volume increased significantly ($P = 0.026$) from the day following administration and body weight decreased ($P < 0.01$) (Fig. 1). BNP decreased significantly post administration of tolvaptan ($P = 0.006$) (Fig 2), as did systolic and diastolic blood pressure. Serum osmolality ($P = 0.001$) and Na level ($P = 0.006$) increased significantly. Urine osmolality also decreased, but the difference was not significant. There were no significant changes in serum blood urea nitrogen (BUN), Cr, estimated eGFR, or other laboratory parameters. Moreover, there was little effect on renal function.

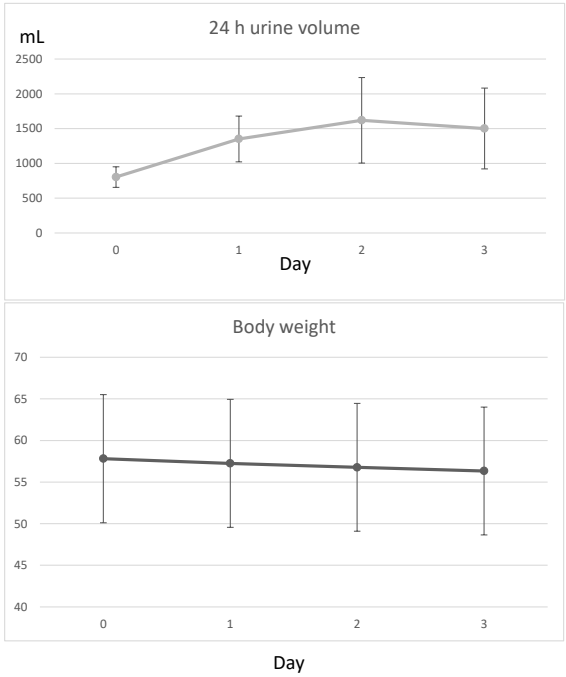

Figure 1. Overall changes in 24-hour urine volume and body weight presented as mean ± SD for the first, second, and third days post-tolvaptan administration.

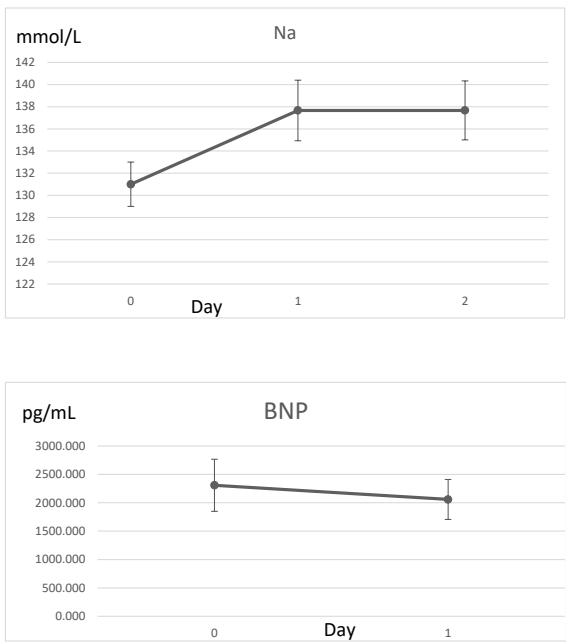

Figure 2. Overall changes in serum sodium (Na) and B-type natriuretic peptide (BNP) levels presented as mean±SD.

Discussion

For patients with HF, fluid volume overload, and hyponatremia, short-term use of a vasopressin receptor antagonist (tolvaptan) is an option for improving serum Na concentration [21, 22]. In this study of patients with severe CKD and CHF, tolvaptan produced a diuretic effect, increased Na level, improved CHF, and reduced body weight and BNP level as early as inpatient day 1 without adversely affecting renal function.

Although congestion is the main reason for admitting patients with worsening acute HF, those presenting with renal impairment may not be able to respond adequately to or to tolerate traditional diuretic therapy. A rapid body weight loss or gain of 1 kg is approximately equivalent to the loss or gain of 1 L of fluid. In this study, we showed that tolvaptan produced a consistent diuretic effect with fluid removal in patients with severe CKD and CHF. Tolvaptan inhibits the binding of arginine vasopressin to the V2 receptors on the collecting ducts of the kidneys, resulting in aquaresis, the electrolyte-sparing excretion of water [22]. If residual renal function remains, tolvaptan, which is a water diuretic that significantly decreases urine osmolality, enables maintenance of the osmoregulation of the body fluids by the renal cortical collecting tubules. In this study, there was residual renal function in nonoligouric patients. We used loop diuretic, furosemide, in combination with tolvaptan, with add on effects of urine amounts and body weight reduction. However, clinically significant hypernatremia did not occur, probably due to the compatibility of furosemide, consistent with the findings of a previous study [20]. BNP provides important information regarding cardiac dysfunction, hypervolemia, and risk of hospitalization or death even in patients with severe impairment of kidney function [23]. A wide range of therapies for HF may lead to reduction in BNP and such changes are typically reflective of improved prognosis [24]. In this study, BNP level decreased significantly after the administration of tolvaptan.

Patients with severe CKD and HF are often at high risk of worsening renal function. A previous study has demonstrated increased renal blood flow after administration of tolvaptan in patients with HF. However, this finding was not observed in patients with renal failure [18]. In the current study, there was no worsening of renal function or deterioration of blood gases or K, Ca, or P levels. The protective function of the kidney initiates a diuretic effect without activating the renin–angiotensin system [25, 26]. Further, no worsening of the serum Cr level may be related to the ameliorated congestive kidney failure due to the diuretic effect of tolvaptan [27]. The effect and mechanism of action of tolvaptan in the maintenance of renal function need to be elucidated.

There are several limitations to this study. This case series study included only a small number of patients and medium- to long-term outcomes were not compared. In addition, there was no dyspnea follow up.

In summary, we examined the additive effect of tolvaptan among patients using loop diuretic, furosemide, for severe CKD complicated by CHF. Urine volume, hyponatremia, and BNP level improved significantly. Free water clearance showed a tendency to increase due to aquaresis effect of tolvaptan. Hypernatremia, worsening renal function, hyperkalemia, metabolic abnormality, hyperphosphatemia, and hypocalcemia did not occur. Patients with severe CKD and HF have high risk of worsening renal function. In this study, tolvaptan presented diuretic effects with free water clearance and no obvious worsening of renal function.

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