

Dual Impact of Tolvaptan on Intracellular and Extracellular Water in Chronic Kidney Disease Patients with Fluid Retention

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Abstract

Objective Tolvaptan, an oral selective V₂-receptor antagonist, is a water diuretic that ameliorates fluid retention with a lower risk of a worsening renal function than conventional loop diuretics. Although loop diuretics predominantly decrease extracellular water (ECW) compared with intracellular water (ICW), the effect of tolvaptan on fluid distribution remains unclear. We therefore examined how tolvaptan changes ICW and ECW in accordance with the renal function.

Methods Six advanced chronic kidney disease patients (stage 4 or 5) with fluid retention were enrolled in this study. Tolvaptan (7.5 mg/day) added to conventional diuretic treatment was administered to remove fluid retention. The fluid volume was measured using a bioimpedance analysis device before (day 0) and after (day 5 or 6) tolvaptan treatment.

Results Body weight decreased by 2.6%±1.3% (64.4±6.5 vs. 62.8±6.3 kg, p=0.06), and urine volume increased by 54.8%±23.9% (1,215±169 vs. 1,709±137 mL/day, p=0.03) between before and after tolvaptan treatment. Tolvaptan significantly decreased ICW (6.5%±1.5%, p=0.01) and ECW (7.5%±1.4%, p=0.02), which had similar reduction rates (p=0.32). The estimated glomerular filtration rate remained unchanged during the treatment (14.6±2.8 vs. 14.9±2.7 mL/min/1.73² m, p=0.35).

Conclusion Tolvaptan ameliorates body fluid retention, and induces an equivalent reduction rate of ICW and ECW without a worsening renal function. Tolvaptan is a novel water diuretic that has a different effect on fluid distribution compared with conventional loop diuretics.

Key words: fluid retention, bioimpedance analysis, extracellular water, intracellular water, tolvaptan, water diuretic

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Introduction

Fluid retention is a frequent and important clinical issue in advanced chronic kidney disease (CKD), because it is a risk factor for end-stage renal disease, cardiovascular disease, and all-cause death (1, 2). Loop diuretics, such as furosemide, are traditionally and commonly used agents for

the treatment of fluid retention; however, these agents are associated with worsening renal failure (3, 4), which is critical in advanced CKD patients. Transient depletion of the intravascular volume is one of the promising mechanisms for worsening renal failure (5). Several studies using bioelectric impedance analysis (BIA), a non-invasive method for the measurement of body composition, have shown that furosemide predominantly lowers extracellular water (ECW),

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Table 1. Baseline Profile of Patients.

No.	Age	Gender	CKD stage	Primary diseases	Tolvaptan (mg/day)	Furosemide (mg/day)	Azosemide (mg/day)	Spirolactone (mg/day)
1	56	Female	5	Diabetic nephropathy	7.5	240	-	-
2	79	Female	4	Nephrosclerosis	7.5	40	60	25
3	78	Female	5	Nephrosclerosis	7.5	20	-	25
4	57	Male	4	Diabetic nephropathy	7.5	20	-	-
5	80	Male	5	Liver cirrhosis	7.5	20	120	-
6	87	Female	5	Liver cirrhosis	7.5	-	60	-

including the intravascular volume, compared with intracellular water (ICW) (6-8).

Tolvaptan, an oral selective V2-receptor antagonist, blocks the effect of arginine vasopressin on renal collecting tubes and results in water diuresis, which ameliorates fluid retention due to heart failure and liver cirrhosis (3, 9-11). Recently, tolvaptan has been used in CKD patients with heart failure, liver cirrhosis and nephrotic syndrome, including diabetic nephropathy (12-16). Unlike loop diuretics, tolvaptan can ameliorate fluid retention with a low risk of a worsening renal function (10). Furthermore, tolvaptan added to conventional diuretic therapy could reduce the risk of a worsening renal function compared with conventional therapy alone (14, 17, 18). A recent review proposed that the mechanism for the favorable action of tolvaptan may be due to the different effect on fluid distribution compared with loop diuretics (5), however, the details remain unclear. We therefore examined the effect of tolvaptan on both ECW and ICW in advanced CKD patients with fluid retention.

Materials and Methods

Patients

This was a prospective study that enrolled 6 advanced CKD patients (stage 4 or 5) with fluid retention, including generalized edema, pleural effusion and ascites. Patients with prior renal replacement or current dialysis were excluded. At enrollment, all patients had been admitted to Nasu Minami Hospital (n=4, Nasukarasuyama, Tochigi, Japan) or Jichi Medical University (n=2, Shimotsuke, Tochigi, Japan) between December 2013 and July 2015, and had received any diuretic treatment except for tolvaptan (e.g., furosemide, azosemide or spironolactone) (Table 1). After enrollment, tolvaptan in addition to conventional treatment was administered to improve fluid retention. We evaluated the effect of tolvaptan for 5 or 6 days, as previously reported (19). The initial dose of tolvaptan in all patients was 7.5 mg/day, and the dosage of tolvaptan and other diuretic treatments remained constant throughout the study. All patients provided their written informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

Blood and urine sample collection

Blood and 24-hour urine samples plus body weight (BW) data were collected before tolvaptan dosing on day 0 and afterwards on day 5 or 6. The blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR), creatinine clearance, serum Na, serum osmolality and urine osmolality were measured. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation coefficients modified for Japanese patients (20).

Measurement of the fluid volume using bioimpedance analysis

Fluid volume analyses were carried out using a BIA device using eight tactile electrodes (InBody S10 or S20; InBody Japan, Tokyo, Japan) (21-23) before (day 0) and after (day 5 or 6) tolvaptan administration, similar to a previous study on furosemide (6). BIA measurements of resistance and reactance were taken with the patient in the recumbent position after 5 minutes of rest using a multifrequency analyzer (1, 5, 50, 250, 500, and 1,000 kHz). ICW, ECW, total body water (TBW: ICW+ECW) and the ratio of ECW to TBW (ECW/TBW) were calculated from the sum of each segment, using the equations in the BIA software program (21, 22).

Statistical analysis

The data are expressed as the mean \pm standard error. The paired or unpaired *t*-test was used to compare variables as appropriate. *p* values of less than 0.05 were considered to be statistically significant. The statistical analyses were performed using the JMP 12 software package version (SAS Institute, Cary, USA).

Results

The baseline characteristics of the 6 CKD patients were as follows: age 72.8 \pm 5.3 years, gender (male 2, female 4), BW 64.4 \pm 6.5 kg, blood urea nitrogen 59.0 \pm 11.1 mg/dL, serum creatinine 3.13 \pm 0.49 mg/dL, eGFR 14.6 \pm 2.8 mL/min/1.73² m, creatinine clearance 13.1 \pm 2.7 mL/min, serum Na 141.0 \pm 0.7 mEq/L, urine volume 1,215 \pm 169 mL/day, serum osmolality 307.6 \pm 2.9 mOsm/kg and urine osmolality 276.6 \pm 19.7 mOsm/kg (Table 1, 2). Primary diseases included neph-

Table 2. Change of Clinical Parameters before and after Tolvaptan Administration.

Characteristics	Before ^a	After ^b	p value
BW (kg)	64.4 ± 6.5	62.8 ± 6.3	0.06
Urine volume (mL/day)	1,215 ± 169	1,709 ± 137	0.03
ICW(L)	20.7 ± 2.8	19.4 ± 2.7	0.01
ECW(L)	15.8 ± 2.5	14.7 ± 2.3	0.02
TBW(L)	36.5 ± 5.3	34.1 ± 4.9	0.01
ECW/TBW	0.43 ± 0.01	0.43 ± 0.01	0.31
Blood urea nitrogen (mg/dL)	58.9 ± 11.1	55.3 ± 10.6	0.23
Serum creatinine (mg/mL)	3.13 ± 1.1	3.16 ± 0.56	0.42
eGFR (mL/min/1.73m ²)	14.6 ± 2.8	14.9 ± 2.7	0.35
Serum Na (mEq/L)	140.0 ± 0.7	141.5 ± 1.1	0.21
Serum osmolarity (mOsm/kg)	307.6 ± 6.3	310.2 ± 4.3	0.21
Urine osmolarity (mOsm/kg)	276.6 ± 43.1	252.8 ± 58.2	0.24

BW: body weight, ICW: intracellular water, ECW: extracellular water, TBW: total body water, eGFR: estimated glomerular filtration rate ^aBefore: day 0 before tolvaptan administration, ^bAfter: day 5 or 6 after tolvaptan administration
Values expressed mean ± SE.

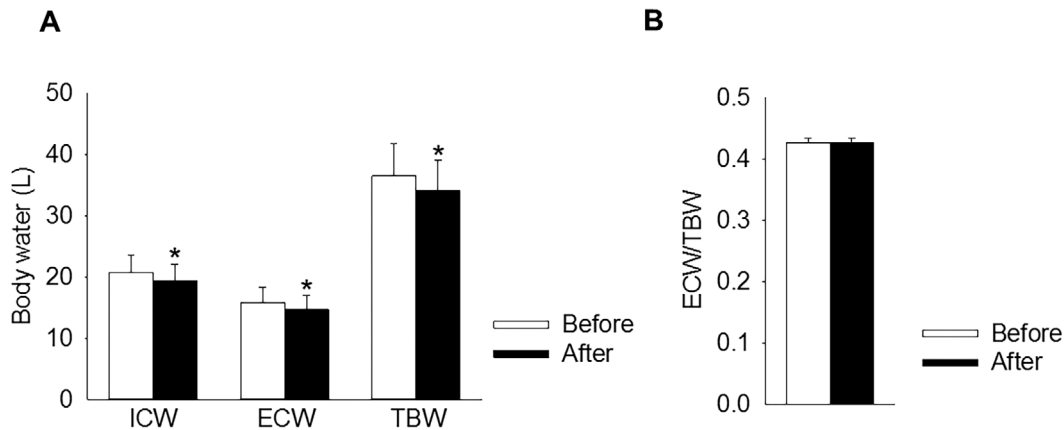


Figure 1. Change in the absolute body water before (day 0) and after (day 5 or 6) tolvaptan treatment (A). BIA showed that tolvaptan significantly decreased ICW, ECW and TBW. The ratio of ECW to TBW (ECW/TBW) was similar among the treatments (B). *p<0.05 vs. before tolvaptan treatment. ICW: intracellular water, ECW: extracellular water, TBW: total body water

rosclerosis (n=2), diabetic nephropathy (n=2) and liver cirrhosis (n=2).

The mean BW decreased by 2.6%±1.3% (64.4±6.5 vs. 62.8±6.3 kg, p=0.06), and the urine volume increased by 54.8%±23.9% (1,215±169 vs. 1,709±137 mL/day, p=0.03) between before and after tolvaptan treatment (Table 2). BIA showed that ICW decreased by 6.5%±1.5% (20.7±2.8 vs. 19.4±2.7 L, p=0.01), ECW decreased by 7.5%±1.4% (15.8±2.5 vs. 14.7±2.3 L, p=0.02), and TBW decreased by 6.9%±1.4% (36.5±5.3 vs. 34.1±4.9 L, p=0.01) (Table 2, Fig. 1, 2). ICW and ECW exhibited a similar reduction rate (6.5%±1.5% vs. 7.5%±1.4%, p=0.32) (Fig. 2), and consequently, ECW/TBW was not significantly changed before and after tolvaptan treatment (-0.48%±0.37%, p=0.12) (Fig. 1, 2). Plasma brain natriuretic peptide (BNP) decreased by 21.4%±13.4% (263.2±197.4 vs. 165.6±99.8 pg/mL, p=0.22, n=3)

and atrial natriuretic peptide (ANP) decreased by 28.3%±11.4% (104.6±29.1 vs. 75.3±23.4 pg/mL, p=0.14, n=3). Blood urea nitrogen, serum creatinine, eGFR and serum Na remained unchanged during the treatment (Table 2 and Fig. 3).

Discussion

In this study, BIA confirmed that tolvaptan ameliorates body fluid retention and induces a similar reduction rate in ICW and ECW without an adverse effect on the renal function, suggesting a novel mechanism for tolvaptan as a water diuretic.

To the best of our knowledge, this is the first study in which BIA detected the amelioration of body fluid retention during tolvaptan treatment. The changes in BW, urine vol-

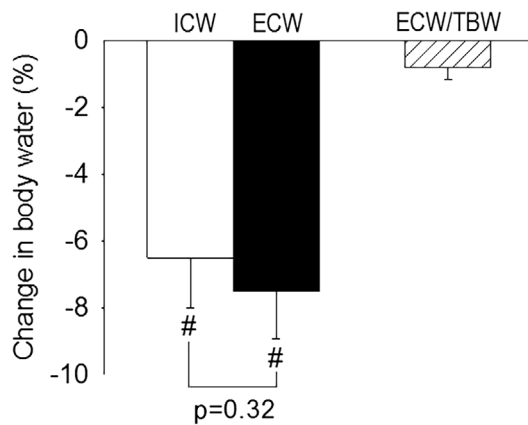


Figure 2. Change in the rate of body water before and after tolvaptan treatment. BIA showed that ICW and ECW significantly decreased by $6.5\% \pm 1.5\%$ and $7.5\% \pm 1.4\%$, respectively. The reduction rate was similar between ICW and ECW. # $p < 0.05$ before vs. after tolvaptan treatment.

ume, and cardiac biomarkers (such as plasma BNP and ANP) have been traditionally used as parameters for the body fluid status and plasma volume (24-26); and recent studies, including ours, showed that tolvaptan ameliorated these parameters (13, 19). However, BW only provides a rough estimate of the body fluid content, and the interpretation of BNP requires a dissection of the relative contributions of baseline cardiac disease and superimposed fluid retention to the elevated BNP level (27). Therefore, an accurate quantitative measurement of the body fluid status in the course of tolvaptan treatment is required. BIA is a useful method to measure the body composition, including TBW, ECW, ICW, fat mass and muscle mass (1, 28). The technique is based on the measurement of the resistance generated in the body against a low voltage electrical current applied by electrodes. The BIA measurement is simple, noninvasive and easy to perform, whereas isotope dilution methods, the gold standard for fluid volume measurement, are time-consuming, expensive, and require multiple blood draws (28). Furthermore, BIA is almost as precise as the dilution methods (28). Therefore, BIA has been widely used in various clinical and animal research settings for the assessment of body composition (28-30). We previously reported that the BIA device InBody is useful for the assessment of the fluid volume and muscle mass in hemodialysis patients (22, 31). We used the same device in this study and revealed the amelioration of fluid retention after tolvaptan treatment.

In this study, tolvaptan equally decreased ECW and ICW, suggesting a quite different mechanism of fluid distribution compared with loop diuretics, because loop diuretics predominantly decrease ECW, but not ICW (6-8). Generally, the primary driving force of fluid movement from the extravascular to intravascular compartment is the oncotic pressure gradient (5). Loop diuretics induce a reduction in the intravascular volume accompanying urinary Na excretion,

and any change in the oncotic pressure would be small. Therefore, the fluid movement from the extravascular to vascular space will be lower. On the other hand, tolvaptan produces free-water diuresis and an increase in serum osmolality (32), which would accelerate the oncotic forces leading to the fluid movement from the interstitial to intravascular compartment (5). An increase in interstitial fluid osmolality may then stimulate a fluid shift from the intracellular to interstitial compartment. These processes may cause a similar reduction rate in ECW and ICW in response to tolvaptan. Unfortunately, we were unable to detect a significant increase in serum osmolality measured 5 or 6 days after tolvaptan administration. We presumed that a rise in serum osmolality and resultant fluid shift from intracellular to interstitial and intravascular spaces would occur immediately after the administration of tolvaptan. Further studies are needed to evaluate these mechanisms.

A potential limitation associated with this study is the small sample size, which might have affected the statistical results, e.g., the change in body water (ICW -6.5 ± 1.5 vs. ECW $-7.5 \pm 1.4\%$, $p = 0.32$). However, the effect of tolvaptan on ICW was obvious, and its effect was clearly different from that of furosemide. Indeed, previous studies using BIA showed that furosemide did not significantly change ICW, although it decreased ECW (6-8). Similarly, we experienced 3 cases (eGFR 38.3 ± 16.9 mL/min/ 1.73^2 m) in whom the administration of furosemide for 7 days (dosage of 26.7 ± 3.0 mg/day i.v.) significantly decreased ECW (-13.3% , $p = 0.027$) but not ICW (-5.7% , $p = 0.072$). In these cases, there was also a different in the reduction rate between ECW and ICW ($p = 0.022$). Therefore, unlike loop diuretics, tolvaptan equivalently acts on ICW and ECW. Further studies with a larger sample size are necessary to confirm our results.

In the present study, loop diuretics were prescribed in all the enrolled patients. Because loop diuretics predominantly decrease ECW (6-8), the effect of lowering ICW in tolvaptan may be underestimated. However, tolvaptan was added to conventional diuretic treatment, and all diuretic agents were administered at the same dosage throughout the study. This protocol may more accurately evaluate the effect of tolvaptan itself on fluid distribution than the simultaneous administration of tolvaptan and other diuretics. On the other hand, two cases in our study had used a potassium-sparing diuretic, spironolactone, along with furosemide. Similar to other cases, the additional administration of tolvaptan on these patients equally decreased ICW (-5.3%) and ECW (-5.9%). Because both tolvaptan and spironolactone act on the collecting ducts, some interaction on fluid distribution may exist, but remains uncertain. Accordingly, comparative studies of single administration of tolvaptan and co-administration with other diuretics, such as furosemide and spironolactone, are required to evaluate the detailed mechanism of tolvaptan on fluid distribution.

The equivalent efficacy of tolvaptan on ICW and ECW may contribute to preserve the renal function. Although loop diuretics have been associated with adverse effects, particu-

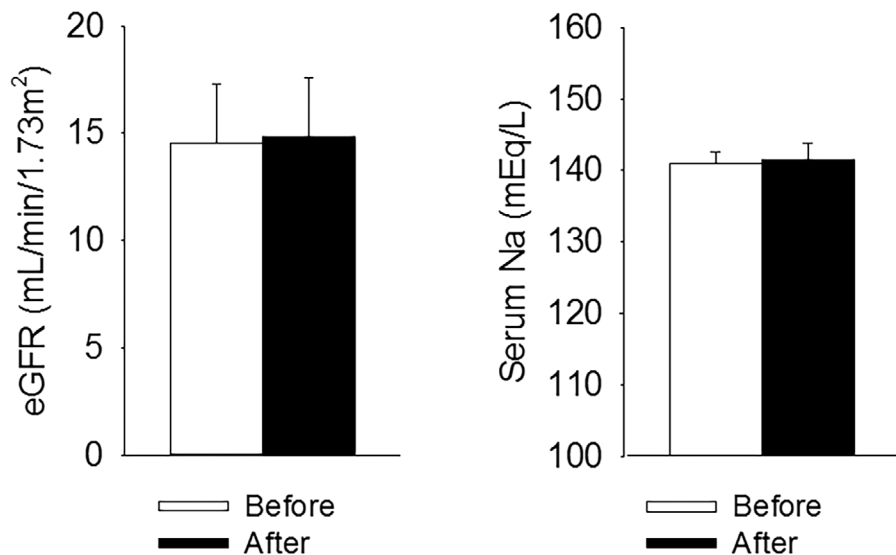


Figure 3. The eGFR and serum Na remained unchanged during tolvaptan treatment.

larly a worsening renal function (3, 4), tolvaptan is an effective water diuretic with no apparent adverse effects on the renal function (13, 15, 17). In this study, tolvaptan administration for advanced CKD patients was also effective for volume control without a worsening renal function. Physiologically, fluid overload results in tissue edema, which induces impaired oxygen and metabolic diffusion, obstructed capillary blood flow and lymphatic drainage, and disturbed cell-cell interactions resulting in the progression of organ dysfunction (27). As an encapsulated organ, the kidney is affected by fluid congestion and increased venous pressures with a disproportionate elevation in intracapsular pressure, which leads to a decreased renal blood flow (RBF) and GFR (33). Tolvaptan has the potential to increase the RBF, whereas furosemide decreases the RBF in patients with congestive heart failure (34). As shown in our study, equivalent removal capability of ICW and ECW by tolvaptan might decrease not only renal interstitial edema but also tubular cell edema, which may lead to the amelioration of an increased venous pressure and result in an increased RBF. Further studies are required to evaluate the association between the renal function and the effect of tolvaptan on fluid distribution.

In this study, all enrolled patients have advanced CKD without dialysis. The worsening renal failure induced by diuretics is critical in these patients. Therefore, we focused on these patients and examined the effect of tolvaptan on the fluid status and distribution. Although we expect that the equivalent efficacy of tolvaptan on ICW and ECW should appear in non-CKD, further studies in patients with a normal renal function are required.

Conclusion

Tolvaptan is a novel water diuretic which has a different effect on fluid distribution compared with conventional loop

diuretics. In this study, BIA confirmed that tolvaptan ameliorated body fluid retention and induced a similar reduction rate in ICW and ECW without an adverse effect on the renal function, suggesting a novel mechanism for tolvaptan as a water diuretic.

The authors state that they have no Conflict of Interest (COI).

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