Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0993-18
Intern Med 58: 639-642, 2019
http://internmed.jp

【 ORIGINAL ARTICLE 】

Tolvaptan Efficiently Reduces Intracellular Fluid: Working Toward a Potential Treatment Option for Cellular Edema

Hiroaki Kawabata[1], Hirotsugu Iwatani[2], Yuko Yamamichi[3], Keiko Shirahase[3], Naoko Nagai[3] and Yoshitaka Isaka[4]

Abstract:

Objective Tolvaptan is a class of diuretics that reduce body water through aquaresis. One of the most prominent characteristics of these agents is that worsening of the renal function is less likely to occur. We investigated the underlying mechanism concerning the change in the intracellular fluid (ICF) when the body fluid is reduced.

Methods In this retrospective observational study, five overhydrated chronic kidney disease (CKD) patients with edema or pleural effusion treated with tolvaptan were assessed by the bioelectrical impedance method twice: once before and once after tolvaptan therapy. The changes in the ICF rate were compared with those in 11 hemodialysis patients undergoing body fluid reduction by hemodialysis.

Results Removal of the body fluid either by tolvaptan or by hemodialysis increased the post/pre-ratio of ICW/total body water (TBW). Tolvaptan reduced the ICF more efficiently than hemodialysis.

Conclusion Tolvaptan treatment lessens body fluid by the efficient reduction of the ICF.

Key words: tolvaptan, intracellular fluid (ICF), extracellular fluid (ECF), bioimpedance, disequilibrium syndrome, cellular edema

(Intern Med 58: 639-642, 2019)
(DOI: 10.2169/internalmedicine.0993-18)

Introduction

Arginine vasopressin is a key regulator of water balance (1, 2). The reduced serum osmolarity typically found in diluted hyponatremia produces an osmotic gradient that promotes the shift of water from extracellular to intracellular compartments. Although many organ systems can tolerate this water shift by increasing the cell volume, the rigid fixed-volume cranium limits the expansion of the brain. Even mild and chronic hyponatremia is reported to be a major independent risk factor associated with falls, and thus impaired attention and gait instability, which are generally considered to be central nervous system-related symptoms, may therefore be associated with hyponatremia (3). This may be because hyponatremia is essentially associated with systemic cellular edema, including brain edema (4-6). Therefore, it is important to improve the disturbed distribution of water between the intracellular fluid (ICF) and extracellular fluid (ECF).

To treat cerebral edema, mannitol or hypertonic saline infusion has been used (5) to drive the shift of water from the ICF to ECF. However, mannitol can cause systemic hypotension, decreased cerebral perfusion or acute kidney injury. As a novel therapy, tolvaptan, a vasopressin V2 receptor antagonist, has received focus because it makes an osmotic gradient by removing electrolyte-free water from the vessels via the kidneys (7). In this way, tolvaptan may restore the water distribution imbalance between the ICF and ECF. However, few reports have so far assessed the effects of tolvaptan on an excessive state of ICF, such as in cases with cellular edema.

To prove our hypothesis, we performed a bioelectrical impedance analysis to estimate the ICF and ECF volumes non-

[1]Department of Nephrology, Higashiosaka City Medical Center, Japan, [2]Department of Nephrology, National Hospital Organization, Osaka National Hospital, Japan, [3]Division of Nutritional Management, Osaka University Hospital, Japan and [4]Department of Nephrology, Osaka University Graduate School of Medicine, Japan
Received: February 10, 2018; Accepted: May 23, 2018; Advance Publication by J-STAGE: November 19, 2018
Correspondence to Dr. Hirotsugu Iwatani, hiwatani-npr@umin.ac.jp

invasively (8, 9). We investigated whether or not tolvaptan could efficiently reduce the ICF by a bioelectrical impedance method.

Materials and Methods

We performed a retrospective observational study of five overhydrated chronic kidney disease (CKD) patients with edema or pleural effusion who were admitted to Osaka University Hospital. They were treated with sodium-excreting diuretics first, with tolvaptan (7.5 mg/day) added on. In 2 cases, the dose of tolvaptan was increased to 15 mg/day. To investigate the relationship between the ICF and the ECF, we measured the impedance before and after the treatment with tolvaptan using an Inbody 720 (Biospace, Tokyo, Japan). As a control, we also measured the impedance of 11 hemodialysis patients twice. The patient characteristics are summarized in Tables 1 and 2. We made a two-dimensional plot of the post/pre-ratio of the intracellular water (ICW) to total body water (TBW) against the amount of the body fluid reduced (-ΔBW) and investigated the relationships in both groups. This study was approved by the Osaka University Hospital Ethics Committee.

We used JMP for statistical analysis. P values less than 0.05 were considered statistically significant. To discern difference in the slopes of regression lines, we performed a covariance analysis.

Table 1. Patient Characteristics of the Tolvaptan Group.

no	age	sex	CKD stage	Underlying disease	Tolvaptan (mg/day)
1	64	F	G4	MPGN, DM	7.5
2	50	M	G5D (PD)	DM	7.5→15
3	56	M	G5D (PD)	Post-nephrectomy due to kidney cancer	7.5→15
4	72	F	G5	RA, heart failure	7.5
5	81	M	G5	DM, liver cirrhosis	7.5

RA: rheumatoid arthritis, DM: diabetes mellitus, PD: peritoneal dialysis, MPGN: membranoproliferative glomerulonephritis

Results

The changes in the clinical parameters by removing body fluid are summarized in Tables 3 and 4. The removal of body fluid either by tolvaptan or by hemodialysis increased the post/pre-ratio of ICW/TBW and decreased the post/pre-ratio of ECW/TBW (Table 5). This indicates that the more the fluid is reduced, the greater the increase in the ICF ratio (Figure). The change in the ICF ratio is dependent on the amount of reduction in body fluid. Of further note, there was a significant difference in the slopes between tolvaptan and hemodialysis (Figure). When the same amount of water is reduced, then the increase in the ICF ratio is greater in hemodialysis than in tolvaptan. In short, tolvaptan suppressed the increase in the ICF ratio to a greater degree than hemodialysis when the body fluid was reduced, thus indicating that tolvaptan reduced ICF more efficiently than hemodialysis.

Discussion

We noted a significant difference in the ICF-reducing

Table 2. Patient Characteristics of the Hemodialysis Group.

No	age	sex	CKD stage	Underlying disease
1	54	F	G5D (HD)	T2DM
2	79	M	G5D (HD)	unknown
3	62	M	G5D (HD)	Nephrectomy due to kidney cancer
4	69	M	G5D (HD)	PKD
5	83	M	G5D (HD)	Nephrosclerosis susp.
6	25	F	G5D (HD)	IgA nephropathy
7	77	M	G5D (HD)	T2DM
8	62	M	G5D (HD)	DM, postliver transplant
9	74	M	G5D (HD)	unknown
10	52	M	G5D (HD)	Diabetic nephropathy
11	57	M	G5D (HD)	IgA nephropathy

PKD: polycystic kidney disease, HD: hemodialysis

Table 3. Changes in the Clinical Parameters in the Tolvaptan Group.

No	BW		ΔBW	ICW/TBW		Post/pre-ratio of ICW/TBW	Cr		Alb		Na		CTR	
	Pre (kg)	Post (kg)	(kg)	pre	post		Pre (mg/dL)	Post (mg/dL)	Pre (g/dL)	Post (g/dL)	Pre (mEq/L)	Post (mEq/L)	Pre (%)	Post (%)
1	48.4	45.7	-2.7	0.586	0.590	1.006826	2.59	2.34	3.3	3.5	141	147	53.4#	-
2	84.4	79.2	-5.2	0.574	0.580	1.010453	9.19	8.41	2.9	3.1	132	139	-	43.0
3	61.1	58.0	-3.1	0.609	0.615	1.009852	13.51	15.74	3.2	3.4	131	135	47.4	47.8
4	40.0	40.1	0.1	0.571	0.571	1.000000	3.97	4.19	3.1	3.2	135	131	*	*
5	58.2	58.3	0.1	0.573	0.572	0.998255	4.15	5.04	4.2	3.5	137	137	58.5	55.3

*The cardiothoracic ratio was unmeasurable due to right massive pleural effusion.

#Right pleural effusion exists.

BW: body weight, CTR: cardiothoracic ratio, -: no data

Table 4. Changes in the Clinical Parameters in the Hemodialysis Group.

No	BW		ΔBW	ICW/TBW		Post/pre-ratio of ICW/TBW	Cr		Alb		Na		CTR	
	Pre (kg)	Post (kg)	(kg)	pre	post		Pre (mg/dL)	Post (mg/dL)	Pre (g/dL)	Post (g/dL)	Pre (mEq/L)	Post (mEq/L)	Pre (%)	Post (%)
1	64.3	52.7	-11.6	0.558	0.596	1.068100	10.59	7.61	2.4	3.2	141	137	54.7	52.7
2	54.5	54.5	0.0	0.601	0.599	0.996672	11.75	10.60	3.5	3.5	136	135	51.4	-
3	57.5	56.7	-0.8	0.606	0.606	1.000000	14.96	13.42	2.3	2.6	136	134	-	52.4
4	62.3	59.2	-3.1	0.596	0.603	1.011745	8.79	6.90	3.5	3.3	139	139	54.0	-
5	56.5	53.7	-2.8	0.582	0.587	1.008591	9.86	7.99	2.9	3.2	140	142	-	-
6	70.5	71.0	0.5	0.619	0.616	0.995153	10.64	-	3.6	-	-	-	-	-
7	64.5	57.5	-7.0	0.564	0.584	1.035461	11.22	8.49	2.8	2.9	138	136	55.3	52.4
8	62.9	62.9	0.0	0.600	0.602	1.003333	2.54	5.52	3.0	3.2	138	137	-	-
9	55.7	54.7	-1.0	0.614	0.611	0.995114	6.30	9.77	3.5	3.2	137	136	53.6	50.6
10	60.6	59.9	-0.7	0.622	0.621	0.998392	10.20	7.43	3.6	3.6	137	138	-	47.2
11	65.9	63.7	-2.2	0.608	0.616	1.013158	8.46	8.18	4.4	3.9	141	143	41.3	-

BW: body weight, CTR: cardiothoracic ratio, -: no data

Table 5. Changes in the Body Weight, ICF Ratio and ECF Ratio by the Body Fluid Reduction.

Group	BW reduction (kg)	post/pre-ratio of ICW/TBW	post/pre-ratio of ECW/TBW
Tolvaptan	2.7 (0.1-4.15)	1.0068 (0.9991-1.0102)	0.9859 (0.9566-0.9963)
HD	1.0 (0-3.1)	1.0033 (0.9967-1.0132)	0.995 (0.9796-1.0050)

Data are expressed as median (interquartile range).
HD: hemodialysis

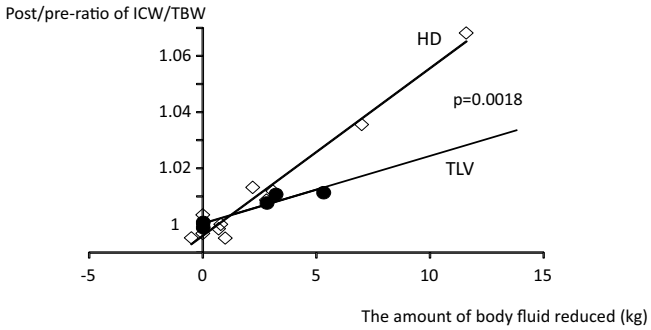

Figure. The relationship between the post/pre-ratio of ICW/TBW and the amount of body fluid reduced. The regression analysis revealed a linear relationship between the post/pre-ratio of ICW/TBW and the amount of body fluid reduced in each group. The regression lines and R^2 and p values are as follows: Y=0.0024X+1, R^2=0.9034, p=0.013 for the tolvaptan (TLV) group (●); Y=0.006X+0.9959, R^2=0.9667, p<0.001 for the hemodialysis (HD) group (◇). A significant difference was noted in the slopes of the regression lines between the two groups (p=0.0018). Body fluid reduction induced by tolvaptan resulted in a milder increase in the post/pre-ratio of ICW/TBW than that induced by hemodialysis.

ability between tolvaptan and hemodialysis. Only a few reports have assessed the change in the ICW/TBW induced by tolvaptan (10). The bioelectrical impedance method allowed us to evaluate the ICW/TBW quantitatively and showed that tolvaptan was able to reduce the ICF by a greater amount and maintain more fluid in the ECF than hemodialysis.

Tolvaptan is a new class of diuretics that enables the excretion of electrolyte-free water from the collecting duct of the kidneys. Through this effect, the serum sodium concentration is slightly upregulated. Because the walls of the vessels are permeable to sodium, when the serum sodium concentration (which equates to the intravessel sodium concentration) is increased, the interstitium sodium concentration is also increased the same amount. This slightly upregulated sodium concentration in the interstitium induces a slight shift in fluid from cells to the interstitium, thereby leading to a decrease in the ICF. This fluid shift from the cells via the interstitium to the vessels and ultimately out of the body via the urine is induced by the electrolyte-free water diuretic properties of tolvaptan. In this way, tolvaptan efficiently reduces the ICF.

The correction of hyponatremia by tolvaptan has been reported to reduce the brain volume and improve cognition in cirrhosis patients (11), a finding that is supported by our results. In contrast, reducing the body fluid by hemodialysis has been shown to result in a severe increase in the ICW/TBW, possibly due to the mechanically forced removal of both fluid and solute from vessels, leading to a lower osmolarity in the ECF than in the ICF, which causes fluid to shift to the ICF. This is consistent with the fact that hemodialysis treatment increases the intracranial pressure, the severe form of which manifests as disequilibrium syndrome (12, 13).

In conclusion, tolvaptan treatment decreases the body fluid by the efficient reduction in the ICF.

Author's disclosure of potential Conflicts of Interest (COI).
Hirotsugu Iwatani: Honoraria, Otsuka Pharmaceutical; Research funding, Otsuka Pharmaceutical. Yoshitaka Isaka: Honoraria, Otsuka Pharmaceutical; Research funding, Otsuka Pharmaceutical.

References

1. Bankir L, Bichet DG, Morgenthaler NG. Vasopressin: physiology, assessment and osmosensation. J Intern Med **282**: 284-297, 2017.
2. Danziger J, Zeidel ML. Osmotic homeostasis. Clin J Am Soc Nephrol **10**: 852-862, 2015.
3. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med **119**: 71.e1-e8, 2006.
4. Gankam Kengne F, Decaux G. Hyponatremia and the Brain. Kidney Int Rep **3**: 24-35, 2018.
5. Walcott BP, Kahle KT, Simard JM. Novel treatment targets for cerebral edema. Neurotherapeutics **9**: 65-72, 2012.
6. Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. Am J Physiol Renal Physiol **295**: F619-F624, 2008.
7. Nathan BR. Cerebral correlates of hyponatremia. Neurocrit Care **6**: 72-78, 2007.
8. McCafferty K, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. Kidney Int **85**: 151-157, 2014.
9. Chlibkova D, Knechtle B, Rosemann T, et al. Changes in foot volume, body composition, and hydration status in male and female 24-hour ultra-mountain bikers. J Int Soc Sports Nutr **11**: 12, 2014.
10. Masuda T, Murakami T, Igarashi Y, et al. Dual impact of tolvaptan on intracellular and extracellular water in chronic kidney disease patients with fluid retention. Intern Med **55**: 2759-2764, 2016.
11. Ahluwalia V, Heuman DM, Feldman G, et al. Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. J Hepatol **62**: 75-82, 2015.
12. Arieff AI. Dialysis disequilibrium syndrome: current concepts on pathogenesis and prevention. Kidney Int **45**: 629-635, 1994.
13. Patel N, Dalal P, Panesar M. Dialysis disequilibrium syndrome: a narrative review. Semin Dial **21**: 493-498, 2008.