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

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Abstract:
Objective  Tolvaptan is a class of diuretics that reduce body water through aquarexis. 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

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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-
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.

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 sus. |
| 6    | 25  | F   | G5D (HD)  | IgA nephropathy       |
| 7    | 77  | M   | G5D (HD)  | T2DM                  |
| 8    | 62  | M   | G5D (HD)  | DM, post liver 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 |
|------|-----|-----|--------|-----------------------------|-----|------|-----|-----|
| 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 | 13.5 | 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
us to evaluate the ICW/TBW quantitatively and showed that the 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).

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

| No | BW | ABW | 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 R² and p values are as follows: Y=0.0024X+1, R²=0.9034, p=0.013 for the tolvaptan (TLV) group (○); Y=0.006X+0.9959, R²=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.
In conclusion, tolvaptan treatment decreases the body fluid by the efficient reduction in the ICF.

Author's disclosure of potential Conflicts of Interest (COI).
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