Beneficial Role of Tolvaptan in the Control of Body Fluids Without Reductions in Residual Renal Function in Patients Undergoing Peritoneal Dialysis

The V2 receptor antagonist tolvaptan has been approved for volume control in heart-failure patients in Japan. Tolvaptan increases renal blood flow, and so the present study was designed to ascertain whether tolvaptan could be a useful diuretic for volume control without reducing residual renal function (RRF) in peritoneal dialysis (PD) patients.

Tolvaptan was administered in 15 PD patients (15 mg daily). Urine volume, body weight, and blood pressure were monitored. Urinary excretion of urea nitrogen Na\(^+\), the osmolality of plasma and urine, and peritoneal and renal Kt/V were analyzed before and after tolvaptan treatment.

In 11 of 15 patients, urine volume increased to more than 400 mL daily. A significant increase in diluted urine was observed, as indicated by a reduction in the specific gravity or osmolality of urine (or both). Urinary excretion of urea nitrogen, and Na\(^+\) was significantly increased. Increases in renal Kt/V were observed, but peritoneal Kt/V was unchanged. Significant increase in creatinine clearance was also observed.

These data suggest that tolvaptan not only stimulates water diuresis, but also natriuresis, without reducing RRF in PD patients. Hence, tolvaptan could be a beneficial tool for the control of body fluid and maintenance of RRF in PD patients.

**Key words**
Vasopressin, V2 receptor, residual renal function

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**Introduction**
Volume overload is commonly observed in peritoneal dialysis (PD). Volume control is one of the major aims in maintenance PD. Preservation of residual renal function (RRF) is also a common aim. The loop diuretic furosemide is typically used in the treatment of heart failure and in PD. Despite the beneficial role of furosemide in controlling volume, reduction of RRF is often observed. Additionally, resistance to furosemide is commonly observed in patients with cardiorenal failure.

The vasopressin type 2 (V2) receptor antagonist tolvaptan is different from loop diuretics (1). Its major mechanism is to inhibit the V2 receptor and localization of aquaporin. However, whether patients with end-stage renal disease (ESRD) can respond to tolvaptan is unknown. The thick ascending limb (TAL) of the loop of Henle, where furosemide acts, is susceptible to ischemia, which is commonly observed in chronic renal failure. In contrast, the collecting ducts, where tolvaptan acts, is relatively resilient with respect to ischemia (2). In addition, tolvaptan has been observed to increase renal plasma flow in patients with chronic heart failure (3).

The foregoing findings led us to hypothesize that tolvaptan has a beneficial role to play in the maintenance of body fluid control without a reduction in RRF. To test our hypothesis, tolvaptan was administered in PD patients with volume overload and heart failure.

**Methods**
The study protocol was approved by the Ethics Committee of Tohoku University Hospital (Sendai, Japan). Written informed consent was obtained from all subjects, and then patients who met all
four of the following criteria were assessed in this prospective study:

- Introduction of PD within the preceding 1 year in Tohoku University Hospital
- Presence of volume overload (defined by edema, blood pressure, cardiothoracic ratio, urine volume, body weight, and ultrafiltration)
- Presence of heart failure diagnosed by symptoms (shortness of breath, edema, and reduced ability to exercise), plasma levels of brain natriuretic peptide, or echocardiography
- Preserved RRF with a urine volume exceeding 100 mL daily

All 15 PD patients who met the criteria were given tolvaptan 15 mg daily. The plasma concentration of sodium (Na\(^+\)), the osmolality of plasma and urine, urine volume, excretion of urea and Na\(^+\), body weight, and blood pressure were monitored. Renal and peritoneal Kt/V (as indicators of renal and peritoneal function respectively) were analyzed before and after (7 days – 3 months) treatment with tolvaptan. Loop diuretics, thiazide diuretics, or aldosterone blockers were also administered in all cases. The doses of those drugs were not changed throughout the study. Food consumption (especially Na\(^+\) intake) was controlled and maintained throughout the study by a dietitian.

Statistical analyses were conducted using the Sigma Plot software application (version 11.0: SPSS, Chicago, IL, U.S.A.). Comparisons of clinical parameters before and after tolvaptan treatment used the paired t-test. The Student t-test was used to compare between-group differences. A value of \( p < 0.05 \) was considered significant.

**Results**

Of the 15 PD patients (age: 44 – 77 years; 11 men; all receiving continuous ambulatory PD) who were the subjects of our study, those who experienced an increased urinary volume of 400 mL or more daily were defined as “responders” and compared with those having a urinary volume of less than 400 mL daily (“nonresponders”). Table I summarizes baseline characteristics and clinical parameters of the two groups at baseline and after treatment with tolvaptan. Although 4 patients were nonresponders, 11 of the 15 (73%) were responders.

Table I

<table>
<thead>
<tr>
<th>Variable(^a)</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ((n))</td>
<td>11</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ((n) men:women)</td>
<td>9:2</td>
<td>2:2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64±11</td>
<td>62±19</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>64.8±14.6</td>
<td>63.4±7.4</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>63.6±13.8</td>
<td>63.6±6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>48±10</td>
<td>49±12</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>6.7±2.0</td>
<td>7.8±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>139±3</td>
<td>140±3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na(^+) (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>296±8</td>
<td>301±1</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>297±5</td>
<td>300±5</td>
<td>NS</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before treatment</td>
<td>174±233</td>
<td>106±132</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>136±370</td>
<td>365±302</td>
<td>NS</td>
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<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before treatment</td>
<td>275±412</td>
<td>–25±763</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>6±439</td>
<td>–258±641</td>
<td>NS</td>
</tr>
<tr>
<td>Ultrafiltration (mL/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>56±19</td>
<td>62±5</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>12±6</td>
<td>11±4</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(a\) Baseline values, and mean ± standard deviation, except as otherwise noted.

\(b\) \(p < 0.05\) compared with before treatment.

NS = nonsignificant.

Furosemide was given to all patients. Thiazide diuretics were administered to 2 responders and 2 nonresponders. Spironolactone was administered to 8 responders and 2 nonresponders. All patients received renin–angiotensin system inhibitors. All patients had elevated concentrations of brain natriuretic peptide in plasma, which averaged 174 ± 233 pg/mL in responders and 106 ± 132 pg/mL in nonresponders, but the difference was not significantly different between the groups. Although small, a significant \( (p < 0.05) \) increase in serum Na\(^+\) was observed from baseline to after treatment, but no significant difference between the groups was observed. Serum osmolality did not change significantly after tolvaptan treatment in either group. Urinary osmolality fell significantly from 269 ± 68 mOsm/kg to 178 ± 29 mOsm/kg in responders \( (p < 0.05), \)
but did not significantly decrease in nonresponders (231 ± 71 mOsm/kg vs. 209 ± 61 mOsm/kg).

Although a small trend toward reduction of body weight was observed in responders, no significant reduction was observed in either group. Urine volume, renal Kt/V, peritoneal Kt/V, daily creatinine clearance (CCr), urinary excretion of urea and nitrogen, and urinary Na⁺ excretion were compared before and after tolvaptan treatment (Figure 1). Urine volume increased significantly (p < 0.05) from 859 ± 341 mL daily to 1950 ± 783 mL daily in responders, but the change in nonresponders (to 1463 ± 229 mL from 1363 ± 354 mL daily) was nonsignificant. A significant (p < 0.05) increase in renal Kt/V to 1.12 ± 0.41 from 0.70 ± 0.35 was observed in responders, but the decrease to 0.66 ± 0.11 from 0.76 ± 0.21 in nonresponders was nonsignificant. Significant changes in peritoneal Kt/V were observed neither in responders (to 0.90 ± 0.26 from 0.90 ± 0.25) nor in nonresponders (to 0.88 ± 0.15 from 0.92 ± 0.16). Daily CCr increased significantly (p < 0.05) to 8514 ± 3308 mL from 6380 ± 3048 mL daily in responders, but the decrease to 5177 ± 948 mL from 5793 ± 950 mL daily in nonresponders was nonsignificant. Urinary excretion of urea nitrogen tended to increase to 2047 ± 1149 mg from 1553 ± 976 mg daily in responders, but a significant reduction to 1630 ± 446 mg from 1975 ± 431 mg daily was observed in nonresponders. Urinary Na⁺ excretion increased significantly to 144 ± 90 mEq from 63 ± 42 mEq daily in responders, but the increase to 109 ± 42 mEq from 101 ± 62 mg daily in nonresponders was nonsignificant.

**Discussion**

In the present study, we set out to determine whether tolvaptan can increase urine volume in patients with ESRD without reducing RRF. In addition, clinical parameters were compared for those who did and did not respond to tolvaptan.

Urine volume increased significantly after treatment with tolvaptan. As indicated by renal Kt/V and daily CCr, RRF was increased after administration of tolvaptan without altering peritoneal Kt/V. Vasopressin stimulates urea transporters, and so, as expected, significant increases in urinary excretion of urea nitrogen were observed (4). Although tolvaptan acts as a diuretic by blocking the V2 receptor, a surprisingly significant increase in urinary Na⁺ excretion was observed. Our study is the first to demonstrate that tolvaptan effectively increases urine volume and increases excretion of urea and Na⁺ without reducing RRF in ESRD patients.

**Increase in urine volume with tolvaptan**

Furosemide is used widely for the control of body fluids in patients with heart failure and renal failure. However, furosemide resistance is commonly observed in such patients. Thus, high doses of furosemide are often used, potentially leading to side effects such as hearing disorders, hyponatremia, and renal dysfunction. In contrast, the V2 receptor-blocker tolvaptan has been used as a diuretic for heart failure in Japan (5). The results of the present study demonstrate that tolvaptan might even increase urine volume in patients with ESRD.

Furosemide is delivered to the peritubular capillary and absorbed through transporters of organic anions. It is secreted in the lumen of proximal tubules and blocks Na–K–2Cl co-transporters in the TAL of the loop of Henle. To stimulate NaCl transport by Na–K–2Cl co-transporters, the TAL requires oxygen in the mitochondria to activate the Na–K ATPase pump, which localizes in the apical side of the TAL. In ischemic renal disease (for example, hypertensive renal injury and cardiorenal failure), the TAL is commonly injured and becomes resistant to the actions of furosemide (6,7). In contrast, tolvaptan is delivered to the peritubular capillaries of the collecting ducts and blocks the V2 receptor. Compared with the TAL, the collecting ducts do not require oxygen transport. Thus, compared with the TAL (where furosemide acts), the collecting ducts are relatively resistant to ischemia. Vasopressin stimulates the transport of water and urea through the V2 receptor, mediated by shuttling of the aquaporin-2 water channel and activation of urea transporters in the collecting duct (1,4). Reabsorption of urea is involved in the increase of osmotic gradients of the medulla and thereby increases water transport (4). Thus, inhibition of the V2 receptor increases the excretion of water and urea. As demonstrated in the present study, tolvaptan increased urine volume and excretion of urea nitrogen in patients with ESRD and with an estimated glomerular filtration rate less than 10 mL/min, suggesting that the V2 receptor is still active in these patients.

The response to tolvaptan was heterogeneous in the present study. We defined a responder as someone who experienced an increase of urine volume to 400 mL or more daily. Although nonresponders did not have a large increase in urine volume, the lowest urinary osmolality was lowered significantly in all patients.
Urine volume may have increased if nonresponders had increased their water intake. Nonresponders had a higher baseline urine volume than responders, and that finding might be one of the reasons that those patients did not experience an increase in urine volume.

In the United States, tolvaptan is indicated for patients with hypervolemic and euvolemic hyponatremia. In Japan, it is indicated for volume control in heart failure. The baseline serum concentration of Na\(^+\) in the present study was not low. Although the serum concentration of Na\(^+\) and serum osmolality increased significantly after treatment with tolvaptan, the level (<8 mEq/L daily) could not induce central pontine myelinolysis because water intake was not restricted in the subjects of the present study and also possibly because they had reservoirs of water and salt in the abdominal cavity.

Although administration of tolvaptan did not show a significant reduction in body weight, that reduction...
was lower than expected despite the significant increase in urine volume. That finding may have been a result of the fact that many of the data in the present study were obtained at 7 days, and water intake was not restricted.

Most of the patients maintained their use of tolvaptan. Long-term administration of tolvaptan (12 months or less) was probably beneficial for avoiding the volume overload commonly observed in PD patients (data not shown).

Possible mechanisms for the increase in RRF and Na$^+$ excretion with tolvaptan
Renal Kt/V and daily CCr were increased in our PD patients taking tolvaptan, but the precise mechanisms of the improvement in those parameters were not determined. However, one clinical study showed that renal plasma flow is maintained and increased by tolvaptan, but that a reduction of renal plasma flow was observed when furosemide was given to the same patients (3).

Surprisingly, Na$^+$ excretion was significantly increased in responders. We did not design the study to determine the mechanisms for that response. However, it can potentially be explained by at least two mechanisms. First, if renal blood flow increases in a way similar to that demonstrated in a previous study (8), Na$^+$ excretion would increase and pressure natriuresis would improve (8). Second, furosemide was administered to all subjects in the present study, and our subjects were, overall, resistant to furosemide because of a reduction in renal blood flow. Tolvaptan might therefore have improved furosemide delivery if renal blood flow was increased.

Limitations of the study
The present study has several limitations. First, the number of the subjects was small, and the study was not randomized. The study was also limited to PD patients whose RRF and urine volume was preserved. Although urine volume was not significantly increased in all patients, we suspect that tolvaptan treatment was beneficial for the control of body water in the responders. Second, although the subjects in the present study had high plasma concentrations of brain natriuretic peptide, the level of heart failure was mostly not beyond New York Heart Association (NYHA) class I. (Only 2 patients were diagnosed as being NYHA III, and 1 patient as NYHA II.) Thus, we do not know if tolvaptan might be beneficial in NYHA IV patients with ESRD. Continuous hemodiafiltration is often used for volume control and reduction of uremia in such patients. Whether PD with tolvaptan treatment could be an alternative treatment requires further study.

Conclusions
Tolvaptan is a useful novel diuretic that could potentially be used to maintain body fluid without altering RRF in PD patients.

Disclosures
TM and SI are consultants to a clinical trial of Otsuka Pharmaceutical. TM has received honoraria for lectures and research funding from Otsuka Pharmaceutical. The Division of Integrative Renal Replacement Therapy is financially supported by Terumo, JMS, and Kyowa Hakko Kirin.

References

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