

Tolvaptan increases urine and ultrafiltration volume for patients with oliguria undergoing peritoneal dialysis

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Abstract

Background Hypoalbuminemia caused by peritoneal dialysate protein loss, frequently occurs in patients on peritoneal dialysis (PD) and is associated with an increased risk of death. We investigate whether PD dialysis exchange volume (PD volume) could be reduced with tolvaptan (TVP) through increased urine volume (UV).

Methods The study included 11 stable patients with oliguria undergoing PD. The following parameters were examined—diuretic response and the effect of TVP on peritoneal ultrafiltration (UF), body weight, serum albumin, sodium, arm muscle area (AMA), PD volume, dialysis efficiency calculator (K_t/V), and urine and serum osmolarity (OSM).

Results The average UV increased from 428 ± 178 to 906 ± 285 mL ($p = 0.018$ by paired t test). Average weekly PD volume decreased from $28,836 \pm 5,699$ to $23,872 \pm 3,569$ mL ($p = 0.04$ by paired t test). Average UF increased from 283 ± 147 to 575 ± 135 mL ($p = 0.019$ by paired t test). On the other hand, there was no significant difference in the average dialysate K_t/V before and after TVP treatment. Serum sodium, AMA, and serum albumin levels were not statistically different before and after TVP treatment. The urine and serum OSM ratio of effective cases before TVP

treatment was higher than that of ineffective cases ($p = 0.024$ by unpaired t test).

Conclusion Our results indicate that TVP is useful for patients on continuous ambulatory PD who have oliguria and high urine osmolarity. Furthermore, we can reduce PD volume to maintain their nutritional status.

Keywords Tolvaptan · CAPD · Urine volume · Ultrafiltration · PD dialysis exchange volume · us-OSM ratio · K_t/V · AMA

Introduction

The use of peritoneal dialysis (PD) has become widespread since the introduction of continuous ambulatory PD (CAPD) over 25 years ago. During this period, many advances have been made and PD is an alternative to hemodialysis (HD), with excellent comparable survival, lower cost, and improved quality of life [1]. Hypoalbuminemia resulting from dialysate protein loss is, however, frequently observed in patients on PD and associated with an increased risk of death [2]. Nevertheless, we usually have to increase the dialysate volume for patients with reduced urine volume (UV), even if they already exhibit hypoalbuminemia.

Tolvaptan (TVP) (SAMSCA; Otsuka Pharmaceutical Co., Ltd), a selective vasopressin V2 receptor antagonist, has recently been available for patients with volume overload in heart failure (HF) when adequate response is not obtained with other diuretics. Recent clinical studies in Japan have demonstrated that short-term TVP treatment increased UV, decreased body weight (BW), and improved signs of fluid overload in patients with HF and excess fluid retention despite receiving loop and/or thiazide diuretics [3–5].

The unique mechanism of TVP action selectively blocks the binding of vasopressin to the V2 receptors (V2Rs) in the

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collecting duct of the kidney. If the V2Rs are left unblocked, the binding of vasopressin with these receptors can cause water retention resulting in hyponatremia. By inhibiting the effects of vasopressin at the V2R, TVP increases the excretion of free water, whereas the excretion of sodium and other electrolytes is not directly affected [6, 7].

Here, we examined whether PD volume could be reduced by increasing UV with TVP.

Method

Protocol

All patients underwent blood and urine tests including neurohumoral assessment, chest X-ray, and echocardiography before TVP therapy. TVP was administered at a low dose of 7.5 mg once daily after breakfast for 2–4 consecutive days. If oliguria persisted we increased the dose to 15 mg daily for >1 month between October 2011 and May 2012 at the Koyukai Memorial Hospital. Background diuretics and other cardiac medications were maintained and water intake was not restricted during the treatment period. Vital signs and UV were measured at baseline and every 8 h on the first day, and every 24 h subsequently. BW was measured every day after urination and before breakfast to the nearest 0.1 kg. A 24-h fluid intake measurement was recorded on the day before and following each treatment day. Blood and urine samples were collected at baseline and every 4 h during the first 8 h after administration of TVP, and every 24 h subsequently. All patients underwent repeated neurohumoral assessment and chest X-ray analysis once a month.

Parameter and laboratory data analysis

BW, UV, PD volume, ultrafiltration (UF), dialysis efficiency calculator (K_t/V), arm muscle area (AMA), and serum concentrations of sodium, potassium, albumin, and urine concentrations of sodium (uNa), potassium (uK), and sodium concentration in PD drainage fluid (PD-Na) were studied immediately before initiation and immediately after one month of TVP treatment in all patients.

Urine and serum osmolarity (us OSM) ratio

We calculated the us OSM ratio as follows:

$$\text{us OSM ratio} = \frac{(\text{urine osmolarity} - \text{serum osmolarity})}{\text{serum osmolarity}}$$

The us OSM ratio was calculated for each individual patient before TVP treatment and 1 month after TVP treatment. The unit of osmolarity is mOsm/kg.

Statistical analysis

Statistical analysis was performed using JMP for Windows software (SAS Institute Inc, Chicago, IL, USA) and Prism 6 for Macintosh software. Results are expressed as mean \pm standard error of the mean. The statistical difference was determined by a 2-sided paired or unpaired Student's *t* test. Differences with *p* value of <0.05 were considered significant.

Results

Patients

This study comprised 11 eligible participants (7 male, 4 female) undergoing PD treatment who had received TVP 7.5–15 mg/day for >1 month between October 2011 and May 2012 at the Department of Immunology and Nephrology of Koyukai Memorial Hospital. The median age of the patients was 78 years (range 52–91 years) (Table 1). In this study, eight of the patients chose automated PD (APD) and the remaining patients chose CAPD. All patients used both 1.5 % glucose dialysate and icodextrin dialysate. Five of the patients had diabetes mellitus (DM) and the remaining patients had nephrosclerosis (NS) as the primary disease. The median levels of sodium, potassium, N-terminal prohormone of brain natriuretic peptide (NT-pro BNP), creatinine clearance rate (CCr), and albumin were 138 mEq/L (range 127–146 mEq/L), 3.86 mEq/L (range 3.2–4.9 mEq/L), 9,615 pg/mL (range 927–40,536 pg/mL), 9.3 mL/min (range 1.2–13.4 mL/min), and 2.4 g/dL (range 1.5–3.4 g/dL), respectively. Furthermore, the median UV was 428 mL/day (range 8–1,417 mL/day) and median total volume of PD dialysate was 28,836 mL (range 6,000–42,000 mL/week). All patients were also medicated with furosemide and three of them were receiving spironolactone as combination diuretics. However, we did not change any drug throughout the study. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Changes in BW, serum sodium, serum potassium, serum albumin, and AMA during TVP treatment

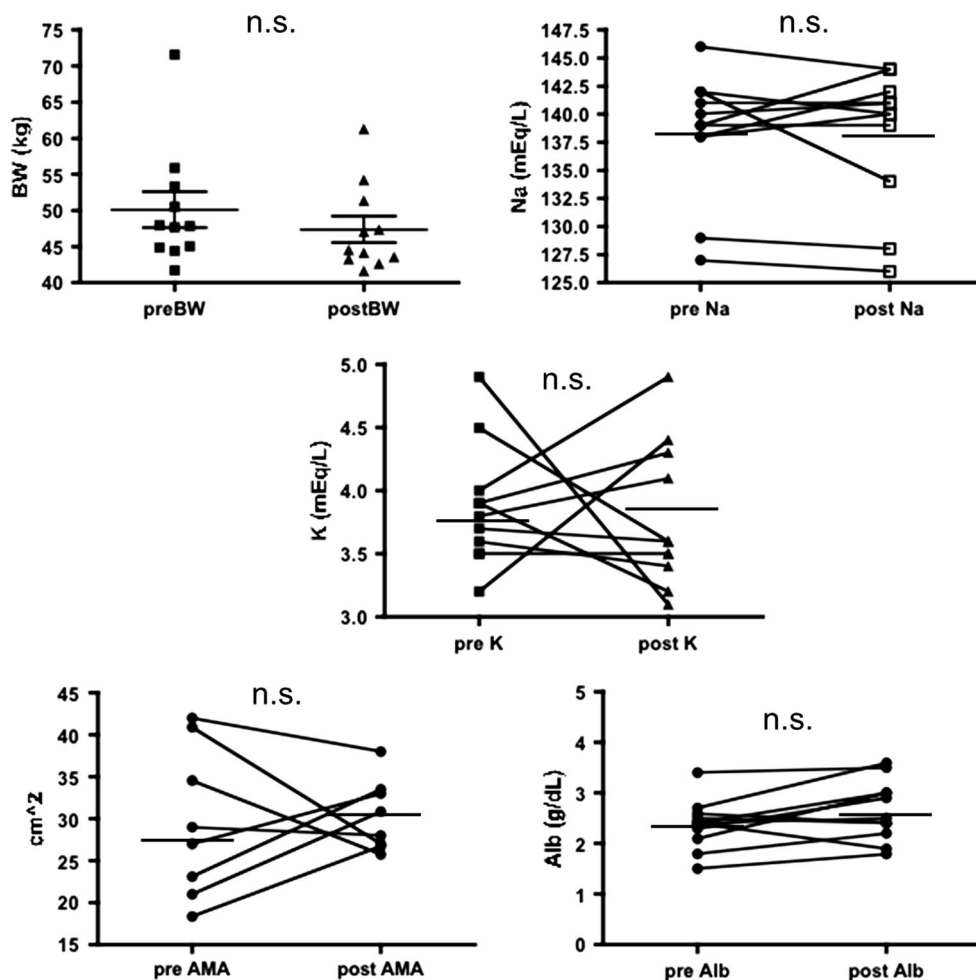
BW decreased from 49.7 ± 8.1 kg to 47.3 ± 5.8 kg after 1 month of TVP treatment, although the difference between pre- and post-treatment BW did not reach statistical significance. Serum sodium, serum potassium, serum albumin, and AMA were not statistically different before and after the initiation of TVP treatment (Fig. 1).

Table 1 Clinical characteristics of CAPD patients treated with TVP

| Case | Age | Gender | PD menu | Primary disease | Na (mEq/L) | K (mEq/L) | NT-pro BNP (pg/mL) | CCr (mL/min) | Alb (g/dL) | UV (mL/day) | Total volume in PD dialysate (mL/week) | Other diuretics |
|------|-----|-----------|--------------------|------------------|------------|-----------|--------------------|--------------|------------|-------------|--|--|
| 1 | 68 | M | APD | DM | 142 | 3.9 | 26,094 | 5.2 | 2.6 | 8 | 44,100 | Furosemide 80 mg Spironolactone 50 mg |
| 2 | 90 | F | APD | NS | 129 | 3.8 | 40,536 | 2.2 | 1.8 | 20 | 33,600 | Furosemide 40 mg |
| 3 | 80 | F | APD | NS | 138 | 4.5 | 7,377 | 11.3 | 3.4 | 400 | 21,000 | Furosemide 40 mg |
| 4 | 61 | M | APD | NS | 146 | 3.9 | 1,880 | 8 | 1.8 | 633 | 31,500 | Furosemide 40 mg |
| 5 | 89 | F | APD | NS | 139 | 3.6 | 8,761 | 35 | 3.1 | 1,417 | 6,000 | Furosemide 40 mg |
| 6 | 87 | M | CAPD | DM | 139 | 3.7 | 1,899 | 1.2 | 1.5 | 283 | 31,500 | Furosemide 20 mg |
| 7 | 91 | M | APD | NS | 140 | 4.0 | 4,142 | 4.3 | 2.5 | 617 | 31,500 | Furosemide 20 mg |
| 8 | 89 | M | CAPD | DM | 138 | 3.2 | 1,844 | 12.9 | 2.4 | 1,000 | 12,000 | Furosemide 60 mg |
| 9 | 52 | M | APD | DM | 141 | 3.5 | 927 | 1.9 | 2.3 | 67 | 36,000 | Furosemide 80 mg Spironolactone 25 mg |
| 10 | 74 | M | CAPD | NS | 142 | 4.9 | 2,566 | 13.4 | 2.8 | 143 | 42,000 | Furosemide 80 mg |
| 11 | 79 | F | APD | DM | 127 | 3.5 | 9,738 | 6.6 | 2.4 | 120 | 28,000 | Furosemide 80 mg Spironolactone 50 mg |
| Mean | 78 | M/F = 7/4 | APD/ CAPD = 8/3 | DM = 5 NS = 6 | 138 | 3.86 | 9,615 | 9.3 | 2.4 | 428 | 28,836 | |

APD automated peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, DM diabetes mellitus, NS nephrosclerosis, UV urine volume

Fig. 1 Comparison of BW, Na, K, AMA, and albumin (Alb) before and after initiation of treatment with TVP, *BW* body weight, *Na* sodium, *K* potassium, *AMA* arm muscle area, *Alb* albumin



Changes in UV, PD volume, UF, and dialysis K_t/V during TVP treatment

The average UV increased from 428 ± 178 to 906 ± 285 mL ($p = 0.018$ by paired t test). The average weekly PD volume decreased from $28,836 \pm 5,699$ mL to $23,872 \pm 3,569$ mL ($p = 0.04$ by paired t test). The average UF increased from 283 ± 147 to 575 ± 135 mL ($p = 0.019$ by paired t test). However, there was no significant difference in average dialysate K_t/V before and after initiation of TVP treatment (Fig. 2).

Changes in uNa and uK, and PD-Na during TVP treatment

uNa decreased from 72.1 ± 26.1 to 47.8 ± 17.7 mEq/L after TVP treatment, although the difference between pre- and post-treatment uNa did not reach statistical significance. uK and PD-Na were not statistically different before and after the initiation of TVP treatment (Fig. 3).

Relationship between UV and us OSM ratio

Figure 4 shows that the us OSM ratio before TVP treatment significantly correlated with delta UV after treatment ($p = 0.0037$, $r = 0.6043$).

Investigation of us OSM ratio

Treatment with TVP was either effective (effective cases) or ineffective (ineffective cases). We defined effective cases as those showing an increase in UV of >400 mL based on mean UV of patients or 2-fold increase in UV compared with UV before TVP treatment. The us OSM ratios of effective cases before TVP treatment were higher than those of ineffective cases ($p = 0.024$ by unpaired t test). The ratios of effective cases decreased from 15.2 ± 10.3 to -6.0 ± 10.6 after TVP treatment ($p = 0.024$ by paired t test). There was no statistical difference between ratios before and after the initiation of TVP treatment in ineffective cases (Fig. 5).

Fig. 2 Comparison of UV, PD volume, UF, and K_t/V values obtained before and after treatment with TVP. *UV* urine volume, *UF* ultrafiltration

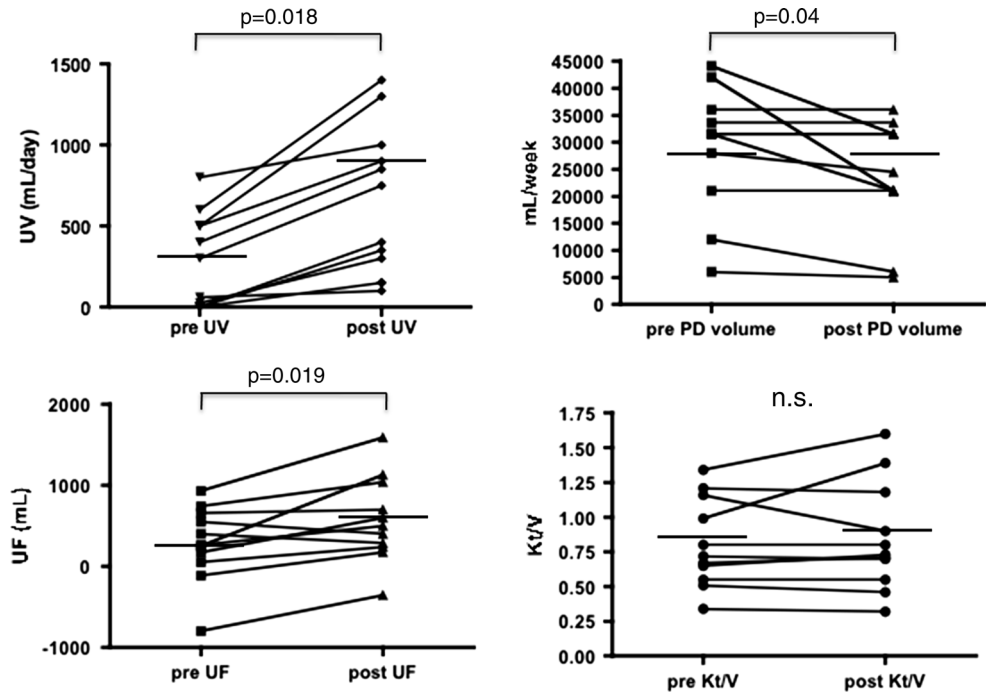
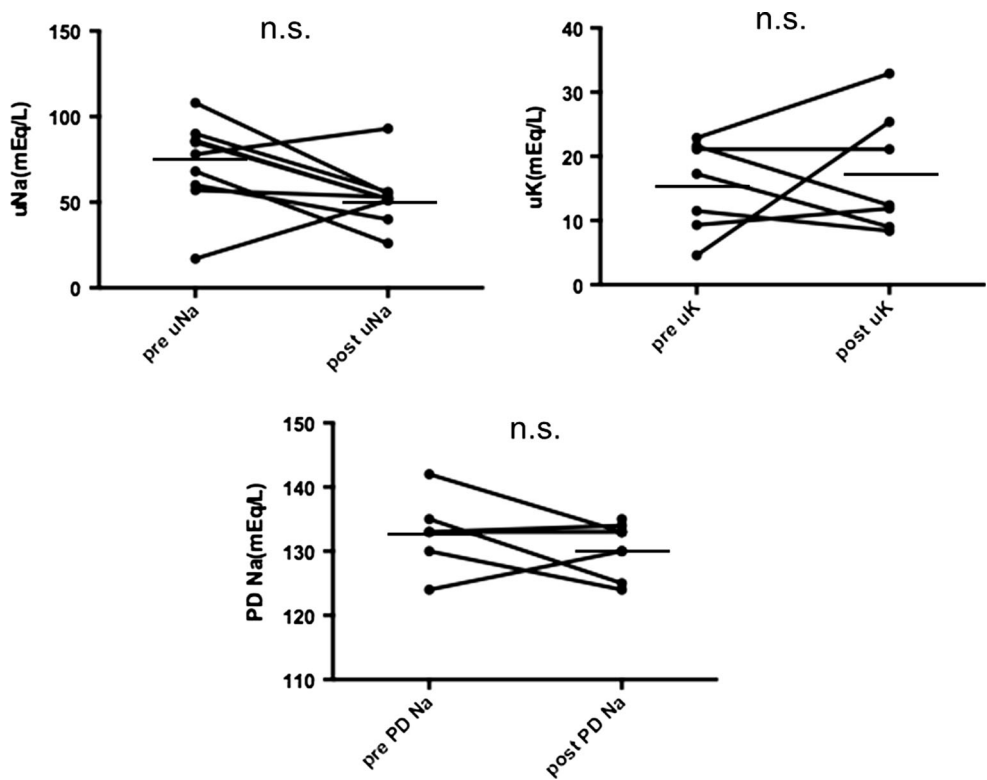


Fig. 3 Comparison of *uNa*, *uK*, and *PD-Na* obtained before and after treatment with TVP. *uNa* urine sodium, *uK* urine potassium, *PD-Na* PD sodium



Discussion

The nutritional and hydration status of patients on CAPD are the most essential aspects of their management because they

influence survival [8, 9]. The survival of patients on CAPD was particularly related to serum albumin [9]. The loss of proteins into dialysate is considered a major limitation of maintenance PD. During maintenance PD, protein loss was

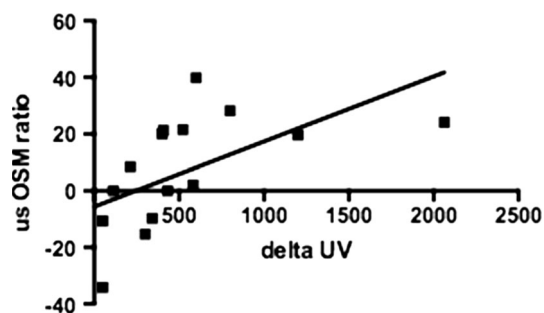


Fig. 4 Correlation between delta UV and us OSM ratio

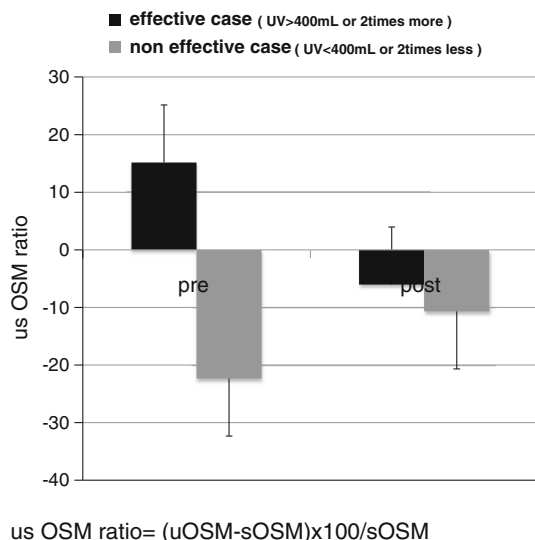


Fig. 5 Comparison of us OSM ratio before and after initiation of treatment with TVP

12.9 g/10 h of dialysis, albumin loss was 8.5 g/10 h, and immunoglobulin G loss was 1.3 g/10 h [10]. The mean peritoneal protein loss was 5.8 ± 2.1 g/day (range 1.9–12.2 g/day) and protein clearance was 0.092 ± 0.041 L/24 h. Serum albumin was the unique parameter among biochemical and anthropometric measurements reflecting nutritional status, correlating with peritoneal protein loss. Peritoneal protein clearance was also not significantly correlated with measurements of visceral protein or somatic nutritional status, except serum albumin [11]. Hakemi et al. [12] showed that older patients on CAPD and patients with low serum albumin are at a high risk of mortality. Patients on CAPD, especially older patients, should have to reduce CAPD volume as much as possible to prevent protein loss. For this purpose, we usually use loop diuretics, thiazide, or spironolactone to increase UV; however, the adverse effects of these drugs limit their use. In particular, the use of high-dose loop diuretics is independently associated with increased mortality [13, 14]. Furthermore, furosemide produces natriuresis, leading to decreased serum sodium levels and

activation of the renin–angiotensin–aldosterone system [15].

The neurohormone arginine vasopressin plays a significant role in the regulation of volume homeostasis, which is mediated by V2Rs in the collecting tubules of the kidney. TVP, a highly selective nonpeptide V2R antagonist, has demonstrated an improvement in volume status, osmotic balance, and hemodynamic profile [16]. TVP increases free water excretion and serum sodium levels while maintaining serum potassium levels. It has not been shown to decrease renal function or the glomerular filtration rate and is well tolerated. In HF, arginine vasopressin worsens HF by causing vasoconstriction of arteries and veins, potentially contributing to remodeling of the left ventricle and causing fluid retention and worsening of hyponatremia [17]. Plasma renin activity increases when furosemide or hydrochlorothiazide (HCTZ) is administered alone, but is unchanged after TVP treatment alone. TVP does not significantly affect the natriuretic activity of furosemide or HCTZ. Furosemide and HCTZ do not significantly affect the aquaretic activity of TVP [18].

On the basis of these data, we used TVP for patients with oliguria on CAPD to not only increase UV but also to reduce dialysis exchange volume.

As shown in Fig. 2, the average UV increased from 428 ± 178 to 906 ± 285 mL ($p = 0.018$ by paired *t* test) and average weekly PD volume decreased from $28,836 \pm 5,699$ to $23,872 \pm 3,569$ mL ($p = 0.04$ by paired *t* test) after TVP treatment without concomitant change in dialysate K_t/V . In terms of PD menu, we did not change the combination of dialysates through this study even though total PD volume was decreased.

These results indicated that TVP was effective for fluid removal and inhibited dialysis exchange volume.

Many patients undergoing CAPD receive antihypertensive agents, including calcium antagonists. As compared with other drugs, azelnidipine increases drain volume by 13 % [19]. Atrial natriuretic peptide may decrease peritoneal fluid absorption, resulting in a significant increase in peritoneal fluid removal and small solute clearances [20]. In our trial, TVP also increased average UF significantly (Fig. 2). On the other hand, we measured uNa, uK, and PD-Na to evaluate if these parameters could help in understanding the mechanism. However, we do not insist on anything in terms of mechanism with these parameters because there was no difference between before and after TVP treatment (Fig. 3).

Arginine vasopressin exerted a local anti-inflammatory effect on the lung through the V2R in a sepsis model [21]. V2R is expressed only in principal cells of the renal collecting duct system, but not on the vascular endothelium or in vascular smooth muscle [22].

TVP treatment can be effective or ineffective, but it is important to determine its effectiveness in advance. We therefore propose measurement of the us OSM ratio before starting TVP treatment. This ratio, calculated as shown above, reflects the concept that patients in whom TVP treatment is effective should have higher urine OSM than serum OSM, despite congestion with high vasopressin levels. A decrease of >26 % in urine OSM from a baseline of >352 mOsm/L for the first 4–6 h predicts responders to TVP [23]. Differences between urine and serum OSM need to be compensated with serum OSM to exclude confounding of the metrics by dehydration. As shown in Fig. 4, there is correlation between UV and us OSM ratio. Based on a mean UV of 428 mL (Table 1), we determined >400 mL of UV as an effective case. Figure 5 shows that TVP-responsive patients had high us OSM ratios compared with nonresponders, and the ratio decreased after TVP treatment, indicating that free water clearance should be increased with TVP. This also means the ratio is useful for determination of efficiency in advance. We re-evaluated each patient to try to identify other factors affecting response to TVP therapy; however, we could not find any factors other than us OSM ratio for predicting response to TVP in advance.

Our results indicate that TVP is useful for patients with oliguria and high urine OSM undergoing CAPD. Furthermore, we can reduce PD volume to maintain their nutritional status.

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Conflict of interest None.

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