Association between plasma concentration of tolvaptan and urine volume in acute decompensated heart failure patients with fluid overload

（論文の要約）

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Association between plasma concentration of tolvaptan and urine volume in acute decompensated heart failure patients with fluid overload

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Abstract

Background: Tolvaptan (TLV) is a useful diuretic for acute decompensated heart failure (ADHF) with fluid overload, but its clinical response vary between patients. The aim of this study is to investigate whether plasma TLV concentrations correlate with the urine volume.

Methods & Results: ADHF inpatients with evidence of fluid overload and total urine volume < 1500 ml 24 hours after initial intravenous administration of 40 mg furosemide were included in the study. On Days 1-7, 7.5 mg oral TLV was added. The plasma TLV concentration, plasma renin activity (PRA), and plasma aldosterone concentration (PAC) were measured on Days 1, 3, and 7. In the 52 patients who completed the protocol, the TLV concentration increased significantly from 67.6±30.1 ng/ml on Day 1 to 98.3±39.6 ng/ml on Day 3 to 144.8±44.2 ng/ml on Day 7, and the TLV concentration correlated with total urine volume on Days 3 and 7 ($r = 0.392$, $p < 0.01$; $r = 0.639$, $p < 0.001$, respectively) but not on Day 1. The urine volume correlated inversely with PRA and PAC ($r = -0.618$, $p < 0.05$; $r = -0.547$, $p < 0.05$, respectively).

Conclusion: Plasma TLV concentrations correlated with the urine volume in chronic-phase but not in acute-phase, which suggest that acute-phase effect of TLV has possibility to be inhibited by renin-angiotensin-aldosterone system activity.

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Introduction

Tolvaptan (TLV), a selective V2-vasopressin receptor antagonist, is known for its excellent diuretic effect [1-4], and it has, in Japan, been essential for intensive treatment of patients hospitalized for acute decompensated heart failure (ADHF) with fluid overload [5-9]. The response to TLV varies and the mechanism of action has been discussed, which may be affected by renal function, anemia and low cardiac output. TLV is an oral drug and thus might also be affected by intestinal absorption. Thus, the purpose of the present study was to determine whether the plasma concentration of TLV differs between the acute phase of treatment and the chronic phase of treatment and whether the plasma TLV concentration is associated with the urine volume in ADHF patients with evidence of fluid overload but without renal dysfunction, anemia, or low cardiac output.

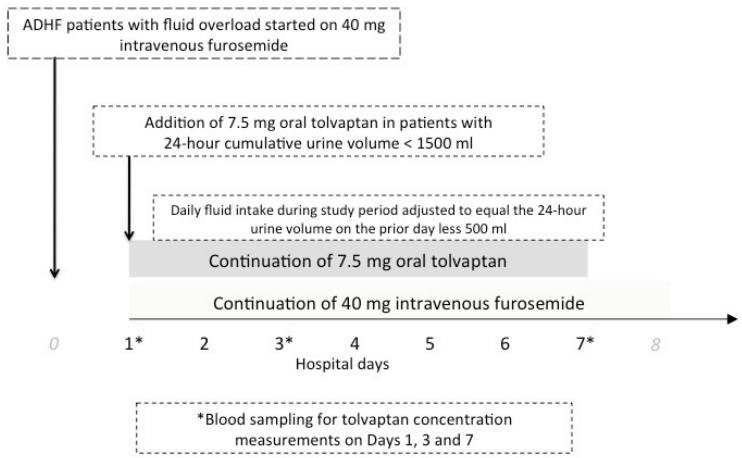
Methods

Patients

Consecutive patients who were admitted to our hospital for worsening congestive heart failure requiring intensive treatment were screened for participation in our study. Patients considered eligible for the study were men and women over 20 years of age with evidence of fluid overload at the time of screening, having orthopnea, edema of the extremities, jugular venous distention defined as jugular venous pressure (JVP) > 10 cmH_2O and/or rales at the base of the lungs. We excluded patients with acute myocardial infarction at the time of admission; patients using any inotropic agent, cardiac mechanical support and/or ventilation including non-invasive positive pressure ventilation; patients on hemofiltration or dialysis; those with pulmonary hypertension due to pre-capillary occlusion; those with systolic blood pressure < 100 mmHg upon admission; those with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2; those with hemoglobin < 10.0 g/ml or a serum sodium concentration > 146 mEq/L; and those from whom we did not obtain informed consent.

Study Design

Patients were screened within 6 hours of hospitalization, and eligible patients were given 40 mg furosemide intravenously until the first morning (Day 0). Patients whose 24-hour cumulative urine volume was > 1500 ml were excluded. For patients not excluded, 7.5 mg TLV was added to the 40 mg furosemide starting on the next morning (Day 1) and continuing for 7 days (from Day 1 to Day 7) (***Figure 1,*** *Schematic representation of the study*



protocol. ADHF = acute decompensated heart failure.). Oral medications that the patients had been taking before hospitalization, including digoxin, any angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker and nitrate, were continued for at least 7 days at the discretion of the attending physician. Patients treated with any inotropic agent or carperitide (recombinant human natriuretic peptide) and any diuretic except intravenous furosemide were excluded for the duration of the study. During the TLV administration period, total daily fluid intake was adjusted to equal the 24-hour urine volume on the prior day minus 500 ml.

Patients' symptoms, graded on a visual analog scale of 0 (worst ever) to 10 (no symptoms); extremity edema, graded as 0 (none) to 4 (severe); jugular venous distention, hepatomegaly and/or hepatojugular reflux were assessed daily by patients' attending physicians after blood sampling. Blood samples for measurement of plasma rennin activity (PRA), the plasma aldosterone concentration (PAC) and the blood concentration of noradrenaline were drawn at 8:00 AM on Days 1, 3, and 7, and patients were required to rest supine on a bed for 30 minutes before samples were drawn. Samples were drawn for the plasma TLV concentration exactly 4 hours after oral administration of TLV. Blood samples were collected in heparinized vacuum tubes, gently mixed, and then immediately centrifuged at 4°C for 15 minutes at 2000g for plasma separation. The plasma was stored at −20°C or below until assay. The plasma TLV concentration was determined by means of a validated high-performance liquid chromatography tandem mass spectrometry method at Toray Research Center, Inc. Details have been described previously [11]. The safety of TLV administration in each case was based on an assessment of the patient's physical signs and symptoms, laboratory tests, and vital signs. The study protocol was stopped if a patient's attending physician advised accordingly. This study was approved by the institutional review board and ethics committee of Nihon University Itabashi Hospital, and it was conducted in accordance with the principals outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Results

Patient Characteristics

Two hundred eighty-six patients met the initial inclusion criteria and were given 40 mg furosemide intravenously until the first morning (Day 0). Ninety-two patients with a cumulative 24-hour urine volume of less than 1500 ml after the administration of furosemide were given 7.5 mg of oral TLV starting on Day 1. Forty patients were dropped from the study (36 patients in whom the symptoms fluid overload disappeared in fewer than 7 days and 4 patients in

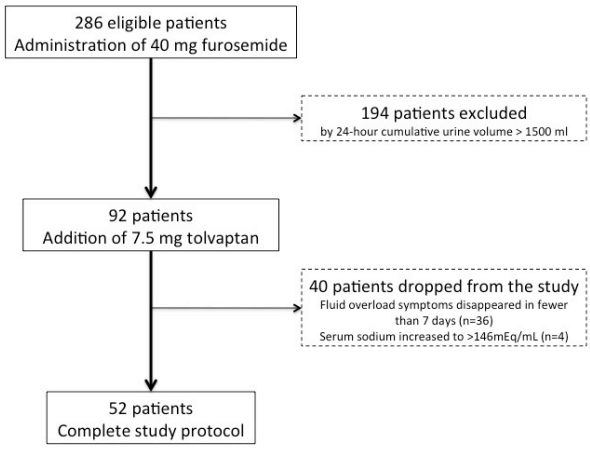


Table 1. Patient characteristics upon enrollment

Age, years	66.4 ± 11.8
Male/female ratio	31/21 (60/40)
Bodyweight, kg	68.0 ± 15.5
Heart rate, bpm	84 ± 18
Systolic blood pressure, mmHg	121 ± 15
Diastolic blood pressure, mmHg	70 ± 9
Etiology of ADHF	
Ischemic heart disease	9 (17)
Dilated cardiomyopathy	19 (37)
Valvular disease	16 (31)
Other	8 (15)
Medical history	
Atrial fibrillation	6 (12)
Hypertension	11 (21)
Dyslipidemia	15 (29)
Diabetes	14 (27)
Oral medications at admission	
Furosemide	46 (88)
Spironolactone	26 (50)
ACE-I	31 (60)
ARB	20 (38)
Beta-blocker	36 (70)
Digitalis	13 (25)
Calcium channel blocker	15 (29)
Statin	9 (17)
Symptoms and results of physical examination	
NYHA functional class, I to IV	III [III-III]
Killip class, 0 to 4	3 [2-3]
Extremity edema, 0 to 4*	3 [2-4]
Jugular venous pressure, cmH_2O	19.3 ± 2.5
Chest X-ray findings	
Cardiothoracic ratio, %	64 ± 9
Pleural effusion	48 (92)
Echocardiographic findings	
Left ventricular ejection fraction, %	42.5 ± 10.5
Left ventricular diastolic diameter, mm	63.7 ± 10.5
Inferior vena cava, mm	23.6 ± 5.3
Moderate to severe MR	17 (33)
TRPG, mmHg	37.5 ± 15.5
Laboratory test results	
Serum creatinine, mg/ml	1.12 ± 0.27
eGFR, ml/min/1.73 m^2	78.8 ± 12.8
Blood urea nitrogen, mg/ml	28.0 ± 11.8
Serum sodium, mEq/l	138.2 ± 4.9
Serum potassium, mEq/l	4.2 ± 0.7
Total bilirubin, mg/ml	1.2 ± 1.1
NT-proBNP, pg/ml	9079 ± 7795
Urine osmolality, mOsm/l	477 ± 167

Data are shown as mean SD, n (%) or median [Q1–Q3] values. ADHF = Acute decompensated heart failure; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NYHA = New York Heart Association; MR = mitral valve regurgitation; TRPG = tricuspid regurgitation pressure gradient; eGFR; estimated glomerular filtration rate; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide. *0 = none, 4 = severe.

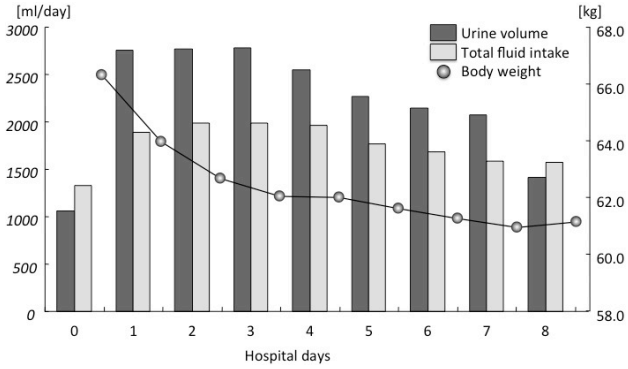
whom the serum sodium level increased to more than 146 mEq/ml). Thus, 52 patients completed the study protocol (***Figure 2**, Flow diagram showing progress of enrollees through phases of the study.*).

Mean age of the 52 patients who completed the protocol was 66.4 ± 11.8 years, the male/female ratio was 31/21, mean systolic blood pressure was 121 ± 15 mmHg and heart rate was 84 ± 18 bpm. Nine (17%) of the patients had ischemic heart disease, and 6 (12%) had atrial fibrillation. Forty-six (88%) had been taking furosemide, and 26 (50%) had been taking spironolactone. All patients had orthopnea, rales at the base of both lungs, edema of the extremities and jugular venous distension defined as JVP > 10 cmH_2O. Mean left ventricular (LV) ejection fraction was 42.5 ± 10.5%, mean LV diastolic diameter was 63.7±10.5 mm and mean diameter of the inferior vena cava was 23.6 ± 5.3 mm, with reduced respiratory movement. The mean serum creatinine level was 1.12 ± 0.27 mg/ml, mean eGFR was 78.8±12.8 ml/min/1.73m^2, mean N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was 9079 ± 7795 pg/ml and mean urine osmolality was 477 ± 167 mOsm/l (Table 1).

Urine Volume and Body Weight

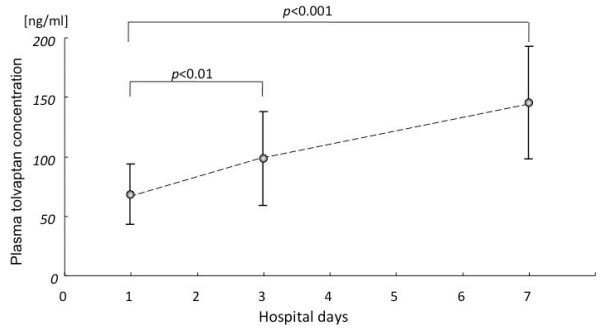
Urine volume increased from 1066 ± 365 ml on Day 0 to 2760 ± 956 ml on Day 1 (***Figure 3**, 24-hour urine volume, total fluid intake and change in body weight over the course of the study (Days 0-8). Note that values were based on the next day's measurements, so for example, 24-hour urine volume shown for Day 1 was actually determined on the morning of Day 2. The graph clearly depicts the significant increase in urine*

volume increased significantly and decrease in body weight decreased after the addition of tolvaptan and that these clinical effects continued until after the tolvaptan was stopped on Day 7.), and body weight decreased steadily through Day 7. The increase in urine volume and the decrease in body weight lessened after Day 4. After completion of the TLV regimen (Day 8), the urine volume decreased significantly and body weight increased slightly in comparison to measures on Day 7.



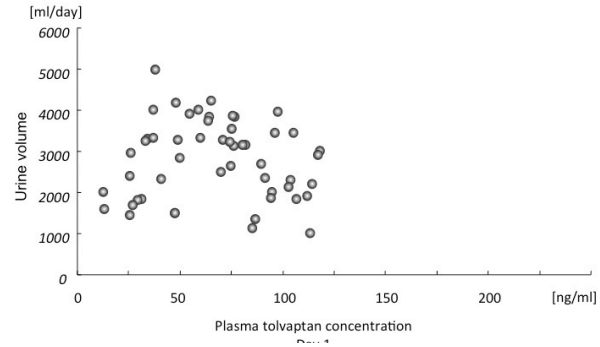
Change in the Plasma Concentration of TLV (Days 1-7)

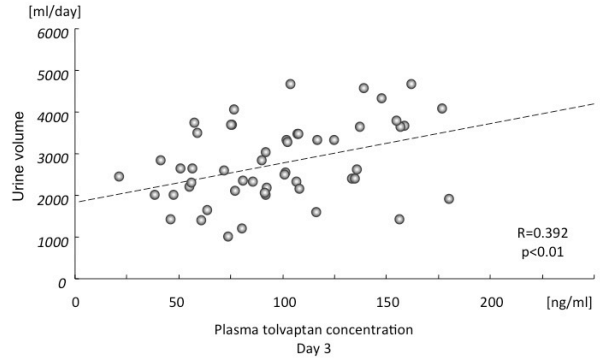
The plasma TLV concentration increased from 67.6 ± 30.1 ng/ml on Day 1 to 98.3 ± 39.6 ng/ml on Day 3 ($p < 0.01$ vs. Day 1) to 144.8±44.2 ng/ml on Day 7 ($p < 0.001$ vs. Day 1), which was approximately twice the Day-1 value (***Figure 4****, Change in the plasma tolvaptan concentration over Days 0-7. Note that the plasma tolvaptan concentration doubled by the end of the 7-day administration.*).

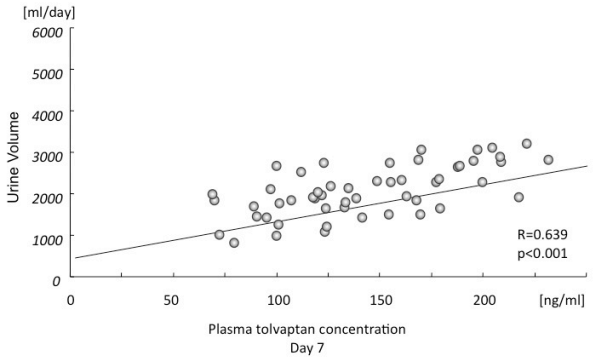


Correlation Between the Urine Volume and Plasma Concentration of TLV

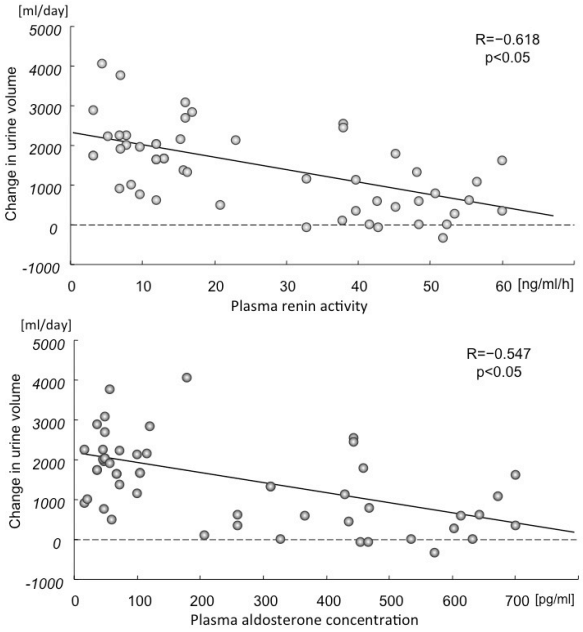
Although there was no relation between the urine volume and plasma TLV concentration and on Day 1, the urine volume correlated significantly with the plasma TLV concentration on Days 3 and 7 ($r = 0.392$, $p < 0.01$; $r = 0.639$, $p < 0.001$, respectively) (***Figure 5****, Relations between the urine volume and plasma tolvaptan concentration on Day 1 (A), Day 3 (B) and Day 7 (C). No relation was observed on Day 1, but correlation was noted on Day 3 (R = 0.392, p < 0.01) and Day 7 (R = 0.639, p < 0.001).*).







Association Between Change in the Urine Volume and Renin-Angiotensin-Aldosterone System (RAAS) Activity in the Acute Phase of Treatment



Change in the urine volume on Day 1 correlated inversely with PRA and PAC, which are indicators of RAAS activity, after administration of TLV ($r = -0.618$; $p < 0.05$, $r = -0.547$; $p < 0.05$, respectively) (***Figure 6*** *Relations between urine volume and PAC (A) and PRA (B) on Day 1. Urine volume after addition of tolvaptan correlated inversely with PAC ($R = -0.547$, $p < 0.05$) and PRA ($R = -0.618$, $p < 0.05$). PAC = plasma aldosterone concentration, PRA = plasma renin activity.*).

Discussion

Change in the Plasma TLV Concentration Over the 7-Day Treatment Course

In our study patients, the plasma TLV concentration was 67.6 ± 30.1 ng/ml on Day 1, 98.3 ± 39.6 ng/ml on Day 3 and 144.8 ± 44.2 ng/ml on Day 7 (Figure 4). The reported peak plasma concentration of TLV in healthy subjects with no swelling of digestive ducts [11] was 135 ± 53 ng/ml after oral administration of 15 mg TLV. This concentration was higher than concentrations in our study patients, probably because of the higher dose of TLV administered and the absence of digestive system swelling. The previously reported plasma concentration of TLV in patients with decompensated heart failure [10] was 92.47 ± 53.58 ng/ml on Day 1 4 hours after oral administration of 7.5 mg TLV and 126.04 ± 40.90 ng/ml on Day 7. The plasma concentration on Day 1 was higher than that in our patients probably because there was no evidence of fluid overload in the previously reported patients. The plasma TLV concentration on Day 7 was lower than that in our patients because digestive system swelling in our patients was greatly reduced by the intensive diuretic therapy. The change in mean body weight of the previously reported patients over 7 days (−1.5 kg) was less than that of our patients (−5.5 kg). Because there was little change in serum osmolality of our patients (from 288.9±11.5 mOsm/kg·H_2O on Day 0 to 291.5±10.5 mOsm/kg·H_2O on Day 1 to 291.69.7 mOsm/kg·H_2O on Day 3 and 288.7 ± 8.6 mOsm/kg·H_2O on Day 7), hemoconcentration was not seen in our patients. Thus, the increase in the plasma TLV concentration can be explained by improved absorbance due to the reduced digestive system swelling achieved with diuretic administration.

RAAS Activity and the Clinical Effect of TLV During Acute-Phase Treatment

In the chronic phase of treatment (Days 3 and 7) for ADHF, the clinical effect of TLV was shown to correlate with the plasma concentration of TLV. This was not true during the acute phase of treatment (Day 1), and then PRA and PAC correlated inversely with the change in urine volume. Neurohumoral factors including RAAS factors increase fluid retention [17]. Angiotensin-II, in particular, increases vasopressin [18, 19], which weakens the effect of TLV somewhat, and aldosterone, which is the final product of the RAAS, increases retention of sodium and water in the renal tubules and is thus thought to act against the effects of TLV [20]. Neither carperitide nor any inotropic agent that would enhance RAAS activity in patients with ADHF was used in this study (Table 2). Therefore, RAAS activity, which is usually observed in patients with ADHF even though they have been given RAAS inhibitors, probably inhibited the effect of TLV. It is logical to assume, then, that inhibition of the RAAS in the acute phase of treatment for ADHF enhances the clinical effects of TLV [21], despite previously reported negative results of standard diuretic therapy [22-24]. Further studies of TLV that will at the same time control for RAAS activity are warranted.

Table 2. Intravenous vasoreactive drugs used by study patients

Inotrope	0 (0)
Vasodilator	49 (94)
Isosorbide dinitrate	47 (90)
Nitroglycerin	2 (4)
Carperitide	0 (0)
Diuretic*	52 (100)

Number (%) of patients is shown.
*Furosemide only, per study protocol.

Limitations

Limitations of our study that may have influenced applicability of our results are as follows: First, we did not directly observe changes in swelling of digestive ducts or of the absorbance of TLV during the week of TLV administration. Second, it is possible that the RAAS had a confounding effect on the urine volume. Third, we excluded patients with low cardiac output on the basis of hypotension rather than invasive measurement of cardiac output. For these reasons, our study findings need to be further explored.

Conclusion

In this clinical study, we found that the plasma TLV concentration increased during treatment and correlated with the clinical effects of the drug during chronic-phase treatment but not during acute-phase treatment, which suggested that the acute-phase effect of TLV has a possibility to be inhibited by RAAS activity.

Conflict of interest: None declared

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