Predictive value of the efficacy of tolvaptan in liver cirrhosis patients using free water clearance

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Abstract. Tolvaptan, an arginine vasopressin V2 antagonist, is available for patients with refractory ascites. Free water clearance was evaluated as a predictor of tolvaptan efficacy. Twenty-one patients with refractory ascites were enrolled in the present study. Liver function test, renal function test, urine volume, free water clearance and osmotic pressure were measured at baseline (day 0) and for each dose of tolvaptan (1.875, 3.75 and 7.5 mg), and compared for efficacy. Tolvaptan increased urine volume and free water clearance decreased osmotic pressure at each dose of tolvaptan, compared to pretreatment levels. Compared to baseline, an increased volume of free water clearance at 1.875 mg of tolvaptan showed a significant correlation with body weight reduction (r=0.480 and P=0.028). Any factors (age, liver function test and renal function test) at pretreatment showed no significant correlation with body weight reduction. An increased volume of urine and osmotic pressure at each dose was not significantly correlated with the tolvaptan effect. Compared to baseline, an increased volume of free water clearance at 1.875 mg of tolvaptan in responders was significantly increased, compared to non-responders (270±241 ml/day: 27±257 ml/day; P=0.042). In conclusion, an increased volume of free water clearance on day 1 was significantly associated with body weight reduction. Free water clearance could be a simple and useful marker for the prediction of tolvaptan efficacy.

Introduction

Ascites is one of the most frequent complications of liver cirrhosis. In total, 5-10% of patients with cirrhosis develop refractory ascites (1,2). Diuretic agents have been used for the treatment of refractory ascites. However, traditional diuretics often complicate electrolyte disorders, such as hyponatremia and hypokalemia. Therefore, solute-free water diuretics are preferable for the treatment of ascites. Recently, tolvaptan, an arginine vasopressin V2 receptor antagonist, was approved in Japan for the treatment of refractory ascites as an anticipated new treatment (3-5). There are controversial studies regarding the predictive factors for the efficacy of tolvaptan in patients with liver cirrhosis (5-7). The present study examined the predictive value of free water clearance for the efficacy of tolvaptan in patients with liver cirrhosis.

Materials and methods

Patients and study design. Twenty-one patients with refractory ascites were enrolled in the study. The characteristics of the patients are shown in Table I. Patients were treated with tolvaptan as follows: 1.875 mg on day 1, 3.75 mg on day 2 and 7.5 mg on day 3. After day 3, the tolvaptan dose was 3.75 or 7.5 mg. Urine volume and free water clearance were measured over 24 h, and urine osmotic pressure was measured at each dose of tolvaptan. The change in body weight from baseline to 2 weeks after initial tolvaptan administration was assessed. Patients who had a weight reduction of >3 kg in 2 weeks were defined as responders.

Measurement of free water clearance. The formula for free water clearance was as described previously (8):

$$\text{Free water clearance} = UV - \text{E-Cosm}$$

$$\text{E-Cosm} = (U_{Na} + U_K) \times UV/P_{Na}$$

where UV is the urine volume over 24 h, E-Cosm is the electrolyte clearance, U_{Na} is the urinary sodium concentration, U_K is the urinary potassium concentration and P_{Na} is the plasma sodium concentration.

Statistical analysis. SPSS version 20.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Comparisons between the two groups were performed using Student's t-test. Correlations were determined using Pearson's

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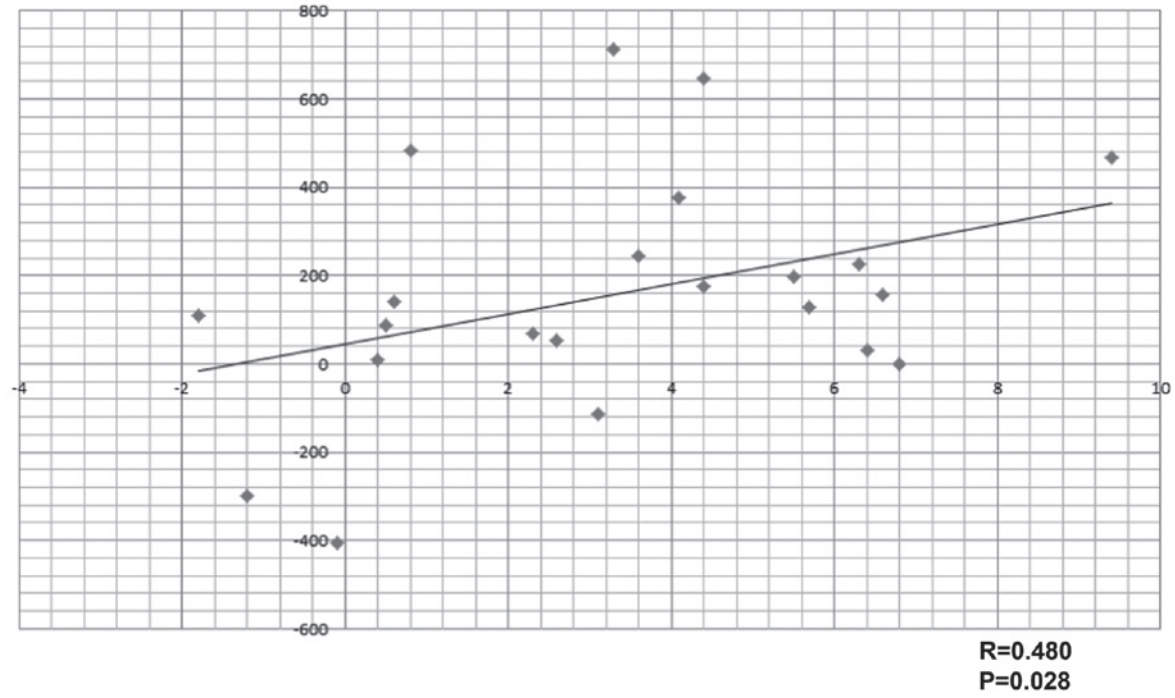

Figure 1. Correlation of free water clearance and body weight reduction. Increased volume of free water clearance on day 1 (1.875 mg) of tolvaptan showed a significant correlation with 2-week body weight reduction (r=0.480 and P=0.028).

Table I. Clinical data of the 21 patients.

Characteristics	Data
Age, years	71.76±7.14
Body mass index	22.9±3.7
Plasma osmolality, mOsm	290.8±20.7
Albumin, g/dl	2.61±0.36
Aspartate transaminase, IU/l	45.4±25.3
Alanine transaminase, IU/l	28.3±20.1
Blood urea nitrogen, mg/dl	23.4±11.2
Cr, mg/dl	1.07±0.60
Na, mEq/l	136.4±2.04
Prothrombin time (%)	59.1±15.6

Data are mean ± standard deviation.

Table II. Correlation of each factor and body weight reduction.

Factors	Correlation coefficient	P-value
Age	-0.014	0.951
Body mass index	0.386	0.084
Plasma osmolality	0.012	0.959
Albumin	-0.014	0.952
Aspartate transaminase	-0.093	0.687
Alanine transaminase	-0.188	0.415
Blood urea nitrogen	-0.355	0.114
Cr	-0.252	0.270
Na	-0.026	0.912
Prothrombin time	-0.237	0.300

linear regression analysis. All the P-values were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Changes in clinical factors following tolvaptan treatment. Tolvaptan increased urine volume and free water clearance at each dose compared to pretreatment levels. Urine volume values were: Pretreatment, 1,363±757 ml; day 1, 1.875 mg, 1,569±616 ml; day 2, 3.75 mg, 1,913±685 ml; and day 3, 7.5 mg, 1,857±750 ml. Corresponding free water clearance values were, respectively: Pretreatment, 332±559 ml; 1.875 mg, 498±521 ml; 3.75 mg, 778±522 ml; and 7.5 mg, 730±621 ml. Osmotic pressures at each dose of tolvaptan were decreased, compared to pretreatment levels. Osmolality values were: Pretreatment, 428±116 mOsm/kg H_2O; day 1, 1.875 mg, 369±138 mOsm/kg H_2O; day 2, 3.75 mg, 364±143 mOsm/kg H_2O; and day 3, 7.5 mg, 285±87 mOsm/kg H_2O.

No factors in pretreatment level showed a significant correlation with body weight reduction after 2 weeks (Table II).

An increased urine volume and decreased osmotic pressure at each dose of tolvaptan showed no significant correlation with body weight reduction after 2 weeks. An increased volume of free water clearance at 3.75 and 7.5 mg of tolvaptan compared to pretreatment did not show a significant correlation with body weight reduction. An increased volume of free water clearance at 1.875 mg of tolvaptan compared to pretreatment showed a significant correlation with body weight reduction (r=0.480 and P=0.028; Fig. 1). There were 12 responders (57%) and 9 non-responders (43%). An increased volume of free water

clearance at 1.875 mg of tolvaptan in responders was significantly increased compared to non-responders (270±241 and 27±257 ml/day, respectively; P=0.042).

Discussion

The present study focused on the predictive value of free water clearance for the efficacy of tolvaptan. Tolvaptan increased the urine volume and free water clearance in a dose-dependent manner. However, urine volume and free water clearance at 3.75 mg of tolvaptan were almost identical to 7.5 mg. In the drug information sheet, the recommended tolvaptan dose is 3.75 or 7.5 mg. According to the study results, 3.75 mg was sufficient.

Any factors (age, liver function test and renal function test) showed no significant correlation with body weight reduction. In previous studies, renal function or liver function affected the tolvaptan effect (6,7,9). These previous studies included severe renal cases or liver failure cases. However, in the present study, patients with relatively mild damage of the renal or liver function were enrolled. This difference may be due to hepatic or renal function severity.

Urine volume at any tolvaptan dose was not significantly associated with free water clearance; only increased volume of free water clearance on day 1 (1.875 mg) was significantly associated with body weight reduction. The majority of cirrhotic patients with refractory ascites have increased levels of vasopressin, which regulate the body water content by modulating renal water excretion (10). Tolvaptan antagonizes V2 receptors and increases free water clearance. Therefore, to evaluate the efficacy of tolvaptan, free water clearance is an improved technique compared to urine volume.

An increased volume of free water clearance on day 2 (3.75 mg) and day 3 (7.5 mg) was not associated with a tolvaptan effect, however, there was a significant association with the volume on day 1 (1.875 mg). Despite an increased volume on days 2 and 3, certain parameters, such as urine volume, plasma sodium, and urine sodium and potassium levels, may be affected when using only 1.875 mg tolvaptan. This result suggested that the initial reaction of tolvaptan could be important.

When the free water clearance was >200 ml/day, 6 of 7 (85%) patients showed a 3 kg body weight reduction. When the free water clearance was <120 ml/day, only 2 of 9 patients (22%) showed a 3 kg body weight reduction. Free water clearance can be calculated using only urine volume, plasma sodium concentration, urine sodium and urine potassium. Therefore, estimating free water clearance is a simple means of predicting tolvaptan efficacy. The present study has certain limitations. The sample size was small and only the effect of short-term administration was assessed. Further large-scale and long-term studies are required to confirm the results.

In conclusion, an increased volume of free water clearance on day 1 compared to baseline was significantly associated with body weight reduction. Free water clearance may be a useful marker for the prediction of tolvaptan efficacy.

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